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# ANNALS of ALLERGY

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ANNALS of ALLERGY

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# THE CLINICAL EVALUATION OF A NEW HISTAMINE ANTAGONIST "DECAPRYN"

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THE present report is concerned with a pharmacological description and clinical evaluation of a new histamine antagonist, Decapryn, which has the chemical name 2-[α-2(dimethylaminoethoxy)-α-methylbenzyl]-pyridine succinate.

## PHARMACOLOGICAL STUDIES

Extensive pharmacological studies on Decapryn have been reported by Brown and Werner.[1] They found the intravenous $LD_{50}$ to be 50 to 60 mg./kg. for mice and rabbits. Subcutaneously in mice and rats and orally in mice, the new compound was roughly one-eighth as toxic as when given intravenously. It was approximately one-fifth as toxic orally in rabbits. Studies in male and female mice and rats indicated acute toxicity was similar for the two sexes.

The new antihistaminic drug was found to have a potent and long action in antagonizing lethal effects of intravenously administered histamine in guinea pigs and to possess a wide margin between effective and lethal doses in this species. Doses of 8 to 32 mg./kg. intravenously protected on the average against 133 to 200 $LD_{100}$'s of histamine and in some individual animals protection was afforded against 320 lethal doses.

Doses of 32 mg./kg. intravenously antagonized four lethal doses of histamine four hours later, and a similar dose subcutaneously antagonized nine lethal doses of histamine six hours later. A dose of 80 mg./kg. orally still afforded protection against seven lethal doses of histamine ten hours after administration.

Decapryn R was developed in the Research Laboratories of the Wm. S. Merrell Company, Cincinnati, Ohio.

A favorable ratio of activity to toxicity was indicated by the determination that minimal effective doses were less than 0.5 mg./kg. intravenously and subcutaneously and 10 mg./kg. orally, while lethal doses were approximately 64 mg./kg. intravenously, 128 mg./kg. subcutaneously, and 640 mg./kg. orally.

The administration of small doses of Decapryn intravenously completely blocked the depressor response of 1 to 4 mcg./kg. of histamine diphosphate in anesthetized cats. Similar doses in anesthetized rabbits completely blocked the typical pressor effects of histamine, indicating that the histamine antagonist effectively antagonizes both arteriolar constriction in rabbits and vascular dilatation in cats.

The effect of Decapryn on the histamine whealing response was investigated in rabbits, and it was found that single and oral doses afforded long protection for this type of antagonism. Doses of 75 mg./kg. completely inhibited the histamine whealing reaction for six hours and partially inhibited it for over eight hours. A smaller dose of 40 mg./kg. partially inhibited whealing for four to six hours and completely inhibited it for one hour.

The succinate salt did not produce corneal anesthesia in rabbits, even in 4 per cent concentration. This was demonstrated to be a matter of penetration of the salt, since alkaline solutions containing the free base produced deep corneal anesthesia.

Decapryn was found to possess a mild antiacetylcholine action. It was nonirritating to rabbit cornea in concentrations up to 4 per cent, and it produced no local tissue damage following subcutaneous and intramuscular injections of 1 per cent aqueous solutions. Three and one-half per cent solutions produced irritation and necrosis following subcutaneous and intramuscular administration. Intravenous injections of doses up to 8 mg./kg. into anesthetized cats, with a reasonably slow rate of injection, produced only slight temporary pressor or depressor effects. Doses of 2 and 4 mg./kg. produced a similar effect when injected rapidly, and the rapid injection of 8 mg./kg. consistently produced a fall in blood pressure which was of short duration.

Brown and Werner[2] have also investigated effects of Decapryn in certain natural and acquired hypersensitivities in laboratory animals. They found that intraperitoneally administered doses of 2 to 4 mg./kg. reduced anaphylactic deaths, in guinea pigs passively sensitized to beef serum, from eight out of nine for controls to three out of seventeen for treated animals.

The new antihistaminic drug was demonstrated to be highly effective in preventing the edema which follows intraperitoneal administration of eggwhite into rats. Twenty out of twenty untreated animals developed a massive edema of the face and paws one and one-half hours after eggwhite administration. At the same time period, massive edema was present in

only two out of twenty-five animals protected with 150 mg./kg. of Decapryn. However, effects of the eggwhite apparently outlasted effects of the single dose of Decapryn, since the incidence of severe edema was similar for both the treated and untreated groups three and one-half hours after administration of the eggwhite. Repeated administration of the antihistaminic agent prevented the development of edema at any time in a large majority of the tested animals.

Experimental dermal sensitizations were developed in guinea pigs by intradermal injection or topical application of chemical antigens known to cause contact dermatitis. Topical applications of Decapryn base in ointment form reduced the severity of lesions resulting from challenging doses of the antigens.

Repeated oral administrations of comparatively large doses of the new antihistamine compound also reduced the severity of lesions and, in addition, markedly reduced the incidence of severe reactions. Smaller doses of Decapryn also gave protection against challenging injections of the chemical antigens, but they were less effective than the larger doses.

The acute toxicity of Decapryn was investigated in animals by Thompson and Werner[3] preliminary to trial of the substance in man. This work was done in dogs, rats, and monkeys.

It was found that oral doses of 7.5 mg./kg. three times daily produced no evidence of toxicity in dogs. Repeated administration of 15 mg./kg. three times daily caused some loss of appetite and weight, mydriasis, apprehension, and muscular tremors in three out of four dogs. None of the doses employed caused hematologic changes or histologic changes in various internal organs.

The apprehension and other toxic signs observed in the three dogs also occurred in one of two monkeys at dose levels of 16 to 20 mg./kg. three times daily. Lower doses produced no toxic effects in either of the two monkeys studied. None of the doses produced blood dyscrasias or visceral damage as determined by peritoneoscopic examination and histologic study of liver biopsy specimens.

The administration of doses as high as 45 mg./kg. twice daily for a period of thirty-eight days had no significant effect on rats, as judged by gross signs of toxicity, hematologic determinations, and histopathology. Repeated administration of increasing doses from 50 to 150 mg./kg. also had no gross toxic effects. However, an increase of 200 mg./kg. resulted in a decrease in the rate of growth in some animals, and an increase to 400 mg./kg. generally caused decreased food consumption and caused one death.

Repeated administrations of Decapryn to rats, in large doses for a comparatively long period, did not lead to tolerance or accumulation; and repeated doses resulted in toxicity only when these doses approached acutely lethal ones.

TABLE I. 123* PATIENTS TREATED WITH DECAPRYN

| Diagnosis | Number | Clinical Response | | | Reactions | | |
|---|---|---|---|---|---|---|---|
| | | Excellent | Moderate | Negligible | Slight | Moderate | Severe |
| Bronchial Asthma | 41 | 8 | 19 | 14 | 7 | 3 | 3 |
| Allergic Coryza | 40 | 29 | 9 | 2 | 4 | 6 | 1 |
| Urticaria | 8 | 7 | 0 | 1 | 2 | 0 | 0 |
| Angioneurotic Edema | 8 | 7 | 1 | 0 | 1 | 0 | 0 |
| Vasomotor Coryza | 7 | 3 | 2 | 2 | 2 | 2 | 1 |
| Atopic Eczema | 6 | 1 | 3 | 2 | 0 | 0 | 0 |
| Infectious Coryza | 2 | 2 | 0 | 0 | 0 | 0 | 0 |
| Migraine | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Generalized Pruritus | 4 | 2 | 1 | 1 | 0 | 0 | 0 |
| Erythema Multiforme | 3 | 1 | 1 | 1 | 0 | 0 | 0 |
| Contact Dermatitis | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Prurigo | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Total | 123 | 62 | 36 | 25 | 16 | 11 | 5 |

*17 patients had mixed or multiple syndromes which did not lend themselves to this tabular analysis.

## CLINICAL STUDIES

For clinical evaluation, 140 consecutive patients (both new and old) were studied in private practice and in two public clinics. The difference in response to medication between private and public clinic patients is well known. The groups, therefore, will be discussed separately. This report is limited to the results seen in the symptomatic treatment of seventy-one private and sixty-nine clinic patients studied in typical allergy practice, requiring relief of their chief presenting symptoms.

*Dosage and Evaluation of Effect.*—We used dosages from 6.25 to 150 mg. four times daily, the latter being employed chiefly in toxicity determinations and in an attempt to evaluate the drug in bronchial asthma, a condition in which antihistaminic agents are, in general, ineffective. Previous studies of antihistaminic agents indicated that the therapeutic dosage was based on the 50 mg. level. However, in view of the pharmacological reports of the comparatively high potency of oral administration of Decapryn, we were prompted to use lower dosage in humans. We found that the usual average dose was 12.5 or 25 mg. In some, the 50 mg. dose was desirable.

The patients were not told that a new drug was being used and were given no information as to the possible pharmacological action or side reactions.

Effects are described as excellent when such relief was so evident that the patient requested the same medication on the next visit. Moderate relief is designated when the patient had some relief, but would be satisfied with more, different or supplementary medication. Negligible relief indicated that no obvious relief was evident.

Side actions are listed as slight, moderate or severe. Of all patients, fifteen had previously taken Benadryl, seventeen had taken Pyribenzamine and sixteen had had both drugs, under the authors' supervision.

*Private Patients (71).*—Bronchial asthma: In this group the highest doses were used, and consequently the highest incidence of reactions was observed. Of thirty-one patients, results were classed as excellent in seven, moderate in fifteen and negligible in nine. Side actions (chiefly drowsiness) were classified as slight in five, moderate in three and severe in two.

Hay fever (allergic coryza): In fourteen patients, excellent relief was obtained in eleven, moderate in three, with slight reactions in one. In five patients with urticaria, four were completely relieved, and there was one who was not relieved with Decapryn, Benadryl or Pyribenzamine. One patient experienced drowsiness. Of four patients with angioeurotic edema, three were completely relieved and (1) moderately relieved. One reported drowsiness. In two patients with atopic eczema, one was relieved completely, the other not relieved.

In two patients with infectious coryza, immediate relief was obtained in both cases. Generalized pruritus was relieved in one-half the patients. Migraine in one patient was completely relieved, and there was significant relief in erythema multiforme and vasomotor coryza.

Multiple or mixed syndromes were observed in eight patients. In six with bronchial asthma and allergic coryza, four were relieved of nasal symptoms, with no effect on the asthma. One was relieved of the allergic, but not the infectious symptoms of the nose. In two patients with bronchial asthma with associated nasal and cutaneous symptoms, the latter two symptoms were completely relieved and there was a slight or moderate effect on the wheezing. There were no side reactions in any of these patients.

*Clinic Patients (69).*—Bronchial asthma: In this group of ten patients, relief was classed as excellent in one, moderate in four and negligible in five. Again, as in the private patient group, there was a fairly high incidence of side actions due to the high dosage employed. Two experienced mild side actions, and one had severe side actions.

Hay fever (allergic coryza): In twenty-six patients, excellent relief was obtained in eighteen, moderate relief in six and negligible relief in two. Reactions were slight in three, moderate in six, and severe in one. As to three patients with urticaria, all were completely relieved, and there was a slight drowsiness in one. Four patients with angioneurotic edema were completely relieved, with no side actions. Of four patients with atopic eczema, three were moderately relieved and one noticed no relief. There were no side actions in this latter group.

Of six patients with vasomotor coryza, two were completely relieved, two experienced moderate relief, and two were not relieved. Side actions in this group were slight in two, moderate in two and severe in one. Generalized pruritus was relieved in one-half the patients. There was significant relief in erythema multiforme and no relief in two patients with contact

dermatitis (poison ivy). There was complete relief in one case of prurigo and temporary relief in one case of migraine.

Multiple or mixed syndromes comprised nine patients in the clinic group. In six patients with bronchial asthma and allergic coryza, excellent results were obtained in both nasal and bronchial symptoms in two, excellent results as to the nose alone in one, moderate relief of the nasal symptoms in two and of the asthmatic symptoms in one. Negligible results were shown in three, moderate drowsiness in one and severe drowsiness in another.

## SUMMARY

Approximately 80 per cent of all allergic symptoms were relieved by Decapryn. Analysis of results showed that 80 per cent of patients with typical hay fever and over 85 per cent of patients with urticaria or angioneurotic edema were completely relieved.

In bronchial asthma, the effects, as with other antihistaminic drugs, are quite unpredictable. Of fifty-four patients, 30 per cent were markedly relieved, 40 per cent were moderately relieved, and in the remainder there was no noticeable relief, although in the group with associated nasal symptoms, a good number were relieved of these latter symptoms.

As to side actions, drowsiness was the most commonly encountered and was observed in about one patient out of six. Of the total number of twenty-three patients reporting disturbing side actions, fifteen were in the asthma group which received comparatively excessive dosage. Reactions in the remaining eight patients were moderate in five and severe in three.

On the basis of a dose of 12.5 to 25 mg., used in treating patients other than the asthmatics, reactions occur much less frequently, probably in fewer than 10 per cent of the treated patients.

Of the patients who had previously taken other antihistaminic agents, one preferred Benadryl, three Pyribenzamine, and of the remainder all but one (who was relieved by none) preferred Decapryn, which, on the basis of these clinical studies, appears to be a valuable addition to the antihistaminic or antiallergic agents now available for the management of allergic conditions.

Further studies on the effects of Decapryn on cutaneous whealing responses and other clinical evaluations are in progress and will be reported upon, separately, in the near future.

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# ALLERGENIC (SKIN-TEST) ACTIVITY OF LOW RAGWEED POLLEN AFTER IRRADIATION OF EXTRACT WITH ULTRAVIOLET LIGHT

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THE purpose of this experiment was to learn whether ultraviolet irradiation, at levels approximating those employed for atmospheric sterilization, exerts any effect upon either the potency or the specificity of pollen extract, as judged by direct and indirect cutaneous tests.

Numerous studies of the effect of ultraviolet rays upon antibodies and antigens have appeared in the recent literature. Kondo[8] investigated the influence of such treatment upon lysin for bacteriophage. Stowens[16] studied the effect of irradiation upon the antigenicity of worm extract. Others have investigated the influence of ultraviolet light upon bacteria (Lea and Haines,[9] and Appling and Tanner[1]), viruses (Levinson,[10] and Henle and Henle[7]), and upon fungi (Emmons and Hollaender.[3]) Hart[4,5] turned the bactericidal action of ultraviolet light to practical use when he employed it to sterilize the atmosphere of operating rooms. Salk, Lavin and Francis,[15] Morgan and Lavin,[13] Levinson[10] and others have inquired into the problem of inactivating bacterial and viral vaccines by exposures which did not reduce the immunological potency of the material. Loss of antigenicity, reported by earlier experimenters, was probably due to heating rather than to irradiation. Casals[2] and Havens et al[6] produced a number of neurotropic viral vaccines which retained their complement-fixing qualities after exposure to ultraviolet light. Antigens prepared with these viruses by usual methods, which involve the use of heat or of chemicals for sterilization, commonly are unsatisfactory for complement-fixation. Repetto[14] observed the effect of ultraviolet rays upon diphtheria toxin, toxoid and antitoxin. Woglom and Warren[17] found that the Shope papilloma virus retained its immunizing power after irradiation.

## MATERIALS AND METHODS

*Preparation of Antigenic Solutions.*—The extract of low ragweed pollen used for these experiments was prepared and irradiated by the Arlington Chemical Company. Irradiation was carried out using a Hygeaire sterilizing unit equipped with a 30-watt General Electric germicidal lamp. The entire unit was inverted over a tabletop in such a manner that the distance between the tube envelope and the tabletop was 6 inches, and solutions placed on the table in small vials or flat dishes received both the direct and the reflected rays from the lamp. According to manufacturers' bulletins, 85 per cent of the radiant energy output of these lamps is confined to the

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wave length 2,537 Ängstrom units. The possibility of ozonolysis is minimized, since ozone production is stated at all times to be below one part in ten million parts of air.

One portion of the extract of low ragweed pollen was subjected to irradiation at 6 inches through a glass barrier for one hour, whereas another portion was similarly treated without the glass barrier and for a period of thirty minutes. The former portion, along with its non-irradiated control solution, had been previously sterilized by passage through a Berkefeld filter, whereas the other solutions were rendered bacteria-free by filtration through sintered glass following the irradiation treatment.

The original extract was standardized upon its nitrogen content, 0.1 mg. of phosphotungstic-acid-precipitate nitrogen representing 10,000 "protein nitrogen" units. Each batch of solution was finally diluted in physiological saline solution to give the following testing strengths per milliliter of extract: .001, .01, .1, 1, 5, 10, and 100 units.

*Technique of Direct Testing.*—Cutaneous tests were performed on the patient's right arm. Using a 0.25 ml. syringe, .02 ml. of antigen in graduated strengths were intracutaneously injected into duplicate sites along the lateral and medial aspects of the arm. The concentrations selected were such as to produce responses ranging from negative to definitely positive, with the aim of establishing the threshold dose after the method of Loveless.[11] The practice of placing one test high in the lateral aspect of the arm and its duplicate lower in the medial portion and using the average as the basis for judgment tends to minimize variation in the reaction to a given dose because of location.

The subjects chosen for direct testing were patients who were pollen-sensitive but untreated for at least ten months. All had received their past therapeutic injections in a limited area of the right arm, which was meticulously avoided during the present experiment, so as to eliminate any residual effect of local immunity.

Twenty minutes after the test solutions had been injected, wheals and their surrounding flares were carefully outlined on the arm in ink. The patterns were subsequently transferred onto tracing paper for later study.

*Procedure for Cross-neutralization Studies.*—An equal volume of serum from an untreated, ragweed-sensitive patient was introduced into each of four sterile Wassermann tubes. Into each tube an equal amount of one of the irradiated antigens, or of its control solution, was added. After mixing, 0.1 ml. from each tube was injected intracutaneously into the back of a normal subject in four successive sites. The next day, one of these four sites was tested with the antigen originally present in the mixture in order to make certain that the site was specifically exhausted. Thereafter, each of the other sites was successively tested with one of the other antigenic solutions and any tendency to react noted.

TABLE I. ALLERGENIC (SKIN-TEST) ACTIVITY OF POLLEN EXTRACT WAS ESSENTIALLY UNCHANGED BY MILD IRRADIATION WITH ULTRAVIOLET LIGHT

| Allergic Patient Tested | Strength of Pollen Extract Eliciting Threshold Response (P. N. Units/ml) | | |
|---|---|---|---|
| | Before Irradiation | After Irradiation | Difference in Threshold Dose |
| | | At 6 inches for 1 hour through glass | |
| 1. Fei | .1 | .1 | none |
| 2. McK | .02 | .1 | questionable |
| 3. Kun | .01 | .02 | not significant |
| 4. Rei | .1 | .02 | questionable |
| 5. Leo | .02 | .01 | not significant |
| 6. You | .02 | .01 | not significant |
| 7. Sha | .1 | .01 | questionable |
| 8. Str | .1 | .01 | questionable |
| 9. Qrk | .001 | .001 | none |
| | | At 6 inches for ½ hour without barrier | |
| 10. Sei | 25 | 10 | questionable |
| 11. Poe | 7 | 5 | not significant |
| 12. Shan | 5 | 5 | none |
| 13. Rei | 5 | 5 | none |
| 14. She | 1 | 5 | questionable |
| 15. Ita | 1 | 1 | none |
| 16. Fri | 1 | 1 | none |
| 17. Cra | 1 | 1 | none |
| 18. Man | 1 | 1 | none |
| 19. Leon | 1 | 1 | none |
| 20. Sbl | 1 | 1 | none |
| 21. McK | 1 | 1 | none |
| 22. Dan | .5 | .5 | none |
| 23. Lur | .1 | .1 | none |
| 24. McKs | .1 | .1 | none |
| 25. Qun | .1 | .1 | none |
| 26. Hen | .5 | .1 | questionable |
| 27. Chr | .01 | .02 | not significant |
| 28. DeR | .01 | .01 | none |

## FINDINGS

Table I shows the approximate threshold doses of irradiated and control solutions tested in twenty-eight allergic patients. In sixteen instances, the results were the same with either solution; in seven others the difference was of questionable significance, and in five of no significance. It was concluded, therefore, that irradiation of low ragweed extract with the doses of ultraviolet light employed had no impressive effect on the allergenicity of the solutions as far as their cutaneous reactivity was concerned. Cross-neutralization experiments led to the same conclusion. Mixtures of reaginic serum and any of the pollen solutions gave rise to immediate wheal and flare reactions when intracutaneously tested in normal subjects, but no further response was noted when the original solution or any of the other solutions was again introduced into the sites on the following day. In other words, irradiated and control solutions behaved in a like manner, which indicated that neither the potency nor the specificity had been grossly altered by exposure to ultraviolet rays.

## SUMMARY AND DISCUSSION

The effect of ultraviolet irradiation upon the skin-test activity of ragweed pollen extract has been tested by establishing the approximate threshold doses of two differently irradiated solutions and of their control, non-irradiated samples, in naturally sensitive cases. No significant differences were noted in the activity of the four specimens, which were derived from one original extraction of pollen. That the potency and specificity of the irradiated samples were essentially unaltered was indicated again by the similarity of results with cross-neutralization tests. The degree of exposure to the rays had been similar to that employed by others for purposes of sterilizing the atmosphere.

Both tests employed by the authors deal with the union of allergen and *reagin*, or sensitizing antibody, as revealed by the urticarial response in naturally sensitive or experimentally sensitized skin. Similar tests could have been carried out in the allergic conjunctiva with a view to determining the relative threshold doses of irradiated and non-irradiated solutions.

Before final conclusions can be drawn regarding the use of ultraviolet irradiation as a means of reducing the chance of atmospheric contamination during routine manufacture of sterile allergens, it will be necessary to determine whether the immunizing powers of these solutions are altered by ultraviolet light. This can be tested by observing the production of thermostable antibodies[12] in either nonatopic or allergic individuals, comparisons being drawn between the control and the irradiated antigen.

The authors wish to thank Mr. Robert A. Harte, of the Arlington Chemical Company, for his preparation and irradiation of the pollen extracts as well as for helpful advice; and Dr. Horace S. Baldwin for his co-operation.

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*(Continued on Page 60)*

# ALLERGIC PROBLEMS OF THE GASTROINTESTINAL TRACT

## Report of Cases Seen in Military Service

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THE important role played by gastrointestinal disturbances in military service is clearly evident from the statistics in the annual reports of the Surgeon General. The report for 1940 ranks gastrointestinal disease as the third cause for admission to sick report, the fourth as a cause of death, and the fifth as a cause for disability.

Diseases referable to the gastrointestinal tract occurring in military and civilian life are essentially the same. If we accept this as a fact, we must more accurately evaluate 18 to 25 per cent of patients diagnosed as suffering from digestive neuroses or functional gastrointestinal disturbances. This percentage of nonorganic gastrointestinal disease is not confined to the hospitals of the United States. Graham and Kerr[5] report that in one military hospital in England 24 per cent of the gastrointestinal cases were functional in nature. Tidy,[15] also of Great Britain, reviewed 2,500 dyspeptic patients admitted to several military hospitals and found that such cases constituted 35 per cent of the total. This large group of patients were placed in the category as having a constitutional psychopathic state or some type of neuroses.

In an article by John L. Kanter, M.D.,[7] Colonel in the Medical Reserve, no mention is made of the probable role played by allergy in the gastrointestinal tract. Rowe,[10] Andresen,[2] Alverez[1] and others have pointed out that, during fluoroscopic studies, allergic reactions will take place in the stomach when milk, chocolate, buttermilk or other foods to which a patient may be hypersensitive are included in the test meal.

The chief clinical forms of allergy are easily recognized. This paper is concerned, however, with those conditions which are definitely allergic but, not being readily apparent, are often troublesome to identify. There are two chief groups of such vague conditions. The first group really comprises the atypical forms of the usually evident allergic complaints, the identifying signs of which are so slight, so indefinite or so involved with the symptoms of complicating conditions that it is difficult to recognize the typical allergic syndrome. The second group is composed of allergic varieties of such conditions as gastrointestinal disturbances, eczema and headache. Here the identification of the allergic status is often confusing since the symptoms are usually indefinite and nonspecific, being frequently shared with nonallergic conditions. It is with the gastrointestinal manifestations as seen in this second group that this paper is concerned.

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Frequently these vague hypersensitive conditions are linked with more definite hypersensitive conditions; the history of an associated bronchial asthma, hay fever or urticaria may be the clue which permits the establishment of the more obscure complaint upon an allergic basis. Again, the presence in the family history, collateral or antecedent, of clinical allergy is of significance since it has been definitely established that the tendency to many forms of the hypersensitive state is an inherited trait. Positive skin tests, scratch or intradermal, very often afford conclusive evidence, but in those individuals in whom the skin tests are negative, the allergic basis may be established by studying the clinical symptoms resulting from a direct test of the patient with the suspected substance. In food problems the "trial and error" method or restrictive diets may be used. Blood eosinophilia and leukopenic index studies may also assist in the diagnosis.

The gastrointestinal manifestations of allergy are caused chiefly by the ingestion of foods, drugs, pollens and bacteria and are due largely to the direct contact of the ingested substance with the mucous membrane, or as a part of the general reaction after the protein has been absorbed through the mucous membrane. They may be due to absorption following inoculation. The severity of these reactions may well be appreciated when one considers the intimate relation of the allergen to the sensitized wall (shock organ) of the alimentary tract.

The allergic gastrointestinal cases may be divided according to whether the reaction was immediate or delayed and/or according to the anatomic location of the reaction.

The *immediate* reaction is exemplified when the time between the ingestion of a food and the reaction varies from several seconds to several hours, and the *delayed* reaction when the time interval varies from four hours to several days. In the first group, the symptoms can never be considered as vague. They are so prompt and usually so intense that the cause and effect are immediately apparent. The acute reaction is exemplified by the patient who is so sensitive that faintness, nausea, vomiting and diarrhea regularly develop within a few moments following ingestion of an allergic food. Substances causing immediate alimentary reactions are apt to be associated with positive skin tests. It is, therefore, justifiable to skin test with all foods, especially in patients who present a strong history of allergy. The offending foods will usually react by skin test.

The delayed reaction is less frequently recognized since it is more obscure. Here the interval between ingestion and reaction is longer, often two or three days or more; the symptoms present are not specific for allergic conditions. The patients who complain of "indigestion" may be considered as presenting this type of reaction.

Rowe[12] and others have classified many symptoms such as anorexia, eructations, pyrosis, epigastralgia, postprandial nausea, vomiting, and abdominal distress, as often associated with gastrointestinal disturbance or

functional states but found in many patients in whom no organic disease was discovered and in whom allergic investigations demonstrated the presence of a food hypersensitivity. Since the longer reaction time confuses the picture, the patient rarely knows the food excitant and, indeed, is often unaware that a food is responsible.

## DIAGNOSIS

The diagnosis of a gastrointestinal allergy necessitates a very careful and detailed history, which may be deceptive because allergic symptoms may resemble those due to actual disease, especially since both conditions may co-exist. When allergy is suspected, it is essential to do thorough gastrointestinal studies. The presence of allergy is to be suspected when the history produces any of the following factors:

1. A family history of allergy, bearing in mind the familial tendency of allergy, and remembering that neither the specific type sensitiveness nor the character of the complaint is inherited, but merely the ability to become allergic.
2. A previous personal history of associated allergic reactions such as recurring skin allergy, recurrent attacks of upper respiratory allergy, so-called sick headaches or migraine and the occurrence of heartburn or diarrhea after certain foods.
3. The occurrence of periodic and vague gastrointestinal symptoms at irregular or regular intervals in institutionalized individuals. (Eating of the same foods on the same day of each week.)
4. The onset of manifestations at a physiological period of life such as puberty, pregnancy, the menopause or after some emotional shock.
5. The diagnosis can be further established by carefully studying the physiological pathology of the manifestations involved. The gastrointestinal manifestations of allergy consist, as in the case of allergy of the upper respiratory tract essentially of two types of reactions: (1) mucous membrane involvement with activity of glands, blood eosinophilia, lymphocytosis and edema; (2) muscular reactions of both spastic and hypotonic character, motivated through the nervous system, mediated perhaps by the formation of a histamine-like substance.

The mucosal manifestations may be mild or quite severe and extensive. There may be local areas of hyperemia about the mouth, esophagus, stomach, intestines, rectum, or generalized reactions throughout the entire gastrointestinal tract, resembling inflammation and producing similar, though at times temporary, reactions.[6,11] Angioneurotic edema may be local or general, invading merely the mucosa or the entire wall. When such reactions affect the intestine or any hollow viscus, symptoms of acute obstruction may appear. Areas of ischemia or edema may occur, resulting in necrosis, ulceration or hemorrhage. At the Cleveland Clinic the above

phenomena have been observed by direct gastroscopic and proctoscopic examinations following the application or injection of the allergen.

Just as in "canker sores," small mucosal ulcers in the mouth may be of short duration. Small gastric or duodenal ulcers may also occur and quickly disappear. There may also be submucosal hemorrhages if the petechial or purpuric areas occasionally seen in the rectum or sigmoid colon break down and bleed. Repeated occurrence of the more severe reactions will finally result in fibrosis, and if chronic irritation constitutes a factor in the production of carcinoma, allergy must be considered as a possible cause of this condition.

The variable muscular manifestations consist of motility disturbances; hypermotility, hypomotility, atony or reverse peristalsis.[3,4] Increased motility may be interpreted as "gas," colic or diarrhea. Diarrhea associated with mucous membrane ulcerations and hemorrhages may give the picture of ulcerative colitis. Hypomotility often associated with a spastic colon may be manifested merely by constipation or, when severe and associated with mucosal changes, may suggest actual obstruction. Spastic contraction may occur in any part of the gastrointestinal tract, and although many are considered as functional states, it is undoubtedly true that an otherwise unexplainable spasmodic condition may be entirely due to allergy. These include esophageal spasm, cardiospasm, pylorospasm, colonic spasm and also anal sphincter spasm. As a rule, the manifestations involving the mucous membrane also extend to the muscular system.

X-ray studies may also be of value in the diagnosis in that they may demonstrate mucous membrane and muscular evidence of allergy. This is especially true if spasticity and hypermotility of the small or large intestine, or the peculiar appearance due to angioneurotic edema of the stomach or intestines, are present as an allergic reaction. Evidences of chronic lesions, such as ulcerative colitis due to prolonged ingestion of offending foods, give the most marked roentgenological pictures and appear similar to those lesions seen as due to other causes.

In gastroscopic examination after the ingestion of the specific antigenic food substances, the characteristic reactions observed are distinct hyperemia, sudden edema of the mucosal folds, presence of grayish mucus and minute hemorrhagic areas and hyperperistalsis.[9] These reactions are suggestive of allergy. Proctoscopically, one may note the development of erythema, edema and occasionally hemorrhage.[14] Pathologically, typical tissue studies may reveal evidence of edema, inflammation, exudation, numerous wandering cells and round cell infiltration with a predominance of eosinophilic cells. Fecal necrosis with ulceration and hemorrhage may also be noted.[8]

Discovering the allergic cause is the major part of the diagnosis. It should be stressed that the presence or absence of skin test reactions is not the one deciding factor in establishing a diagnosis of allergy. It is frequently true that the presence or absence of skin reactions is of para-

mount value only when interpreted in relation to a specific type of allergy and the present clinical problems. It is essential in each instance to prove the clinical relationship of the supposedly causative substances. It is necessary for the patient to keep a careful record of all foods or drugs ingested together with notes on symptoms in relation to the contact with these foods and drugs. It must be understoood that whenever a small quantity of food or other item to which a patient is hypersensitive is ingested, a reaction will result, and that one food alone is rarely responsible in a given case.

### TREATMENT

The treatment of gastrointestinal allergy consists of:

1. The relief of the acute attack.
2. The prevention of future attacks.

In relief of acute attacks where an acute surgical abdominal emergency is suspected and operation considered, it may be desirable to apply some harmless therapeutic measure which would increase gastrointestinal motility and, at the same time, not endanger the patient's life. The drug of choice is, of course, epinephrine (1:1,000) in doses of 0.3 to 0.5 c.c. subcutaneously. This has been known to produce spectacular results. Ephedrine (3/8 grain) has been used orally to good advantage following the immediate acute attack. Pituitrin, calcium and parathyroid have been used with moderate success in some instances when epinephrine has failed or proven undesirable.

In those cases where the acute reaction is known to be allergic and due to food factors, lavage, catharsis, enemata or intravenous fluids (especially glucose saline) may be of value. Castor oil and magnesium sulphate are the excellent cathartics for this purpose.

In the prevention of future attacks following recovery from the acute attack, a complete allergic survey is essential. The subsequent care of the patient in respect to desensitization and dietary restrictions must then be governed by this allergic examination.

Physicians interested in allergy[13] have suggested diets of different types, with varying degrees of success. Experience has proven that success in the solution of an alimentary allergy depends on a co-operative patient, and then only when the patient has been intelligently advised of the principles underlying the restrictions and additions regarding the various allergens. Here, too, the physician must remember that too restricted diets over long periods may do greater harm than good, and his ingenuity will be taxed to the utmost to advise both a palatable and a physiologically complete diet.

The following five cases were merely typical of the larger number seen in the allergy clinic and in consultation with the Gastrointestinal Section. The first two cases, were of more than usual interest because of their similarity to conditions other than allergy and are, therefore, presented in

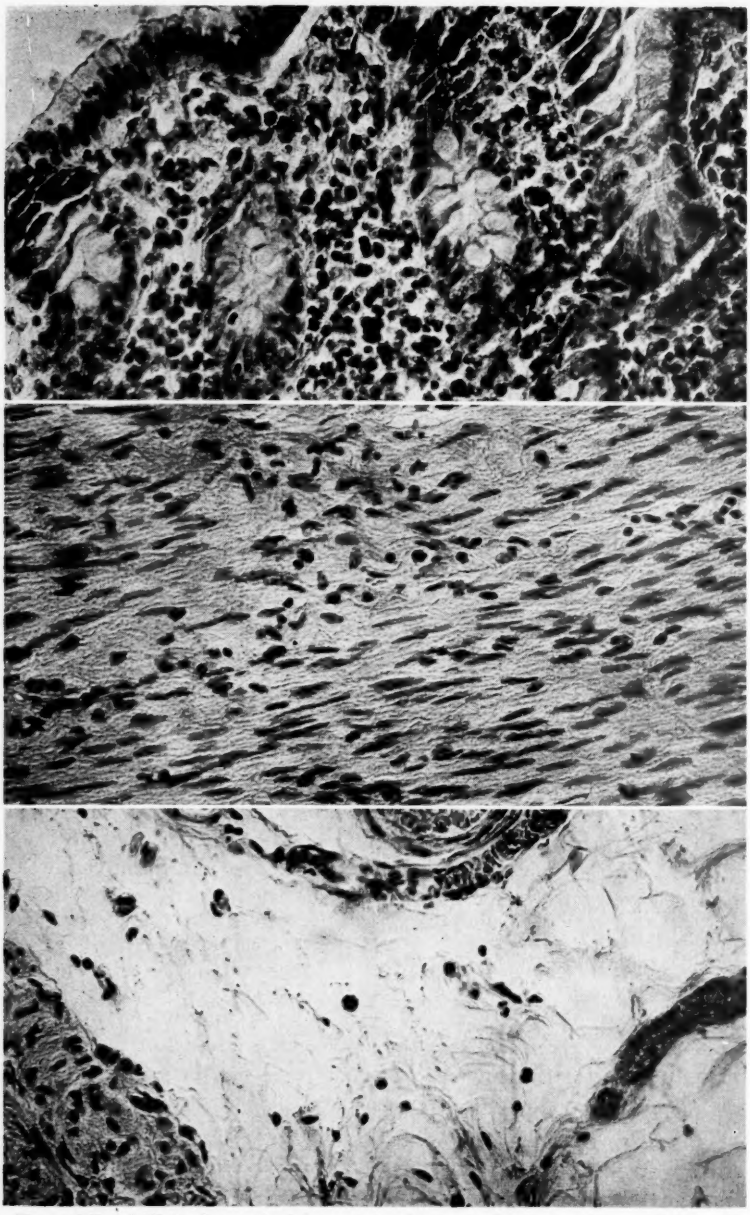

Fig. 1. *(Above)* Photomicrograph shows mucosa with some edema, numerous wandering cells, eosinophil cell colonies.
*(Center)* Photomicrograph shows muscle with edema and round cell infiltration, eosinophil cells predominating.
*(Below)* Photomicrograph shows serosa, with congestion and edema, some round cell infiltration containing eosinophiles.

more detail and with photomicrographs. From January, 1943, to January, 1946, the Allergy Section saw 197 patients having symptoms referable to the gastrointestinal tract, of whom 163 had complete gastrointestinal studies with negative findings. Of these, 118 (60 per cent) had from fair to excellent relief following allergy studies and treatment.

## REPORT OF CASES

*Case 1.*—A woman, aged twenty-one, presented a history of recurring attacks of bronchial asthma mild in degrees for a period of ten years. Her father suffered from bronchial asthma. Six months previously she had had an acute attack of right lower quadrant pain and other clinical signs of acute appendicitis, except for a normal polymorphonuclear count and an 18 per cent eosinophilia. No operation was performed. Subsequent differential counts revealed a gradual return of the eosinophilia to normal limits. Three months following the first attack, a second attack similar to the first was experienced, and while undergoing allergy studies, a third attack occurred. At this time the differential blood count revealed a polymorphonuclear count of 7,800 and an eosinophilia of 23 per cent. The clinical impression was acute allergic appendicitis. Because of the frequency of attacks and the dangers of obstructive symptoms which could develop due to prolonged edema in the presence of an associated fecalith, an appendectomy was performed.

Pathologically, a histological diagnosis of allergic appendicitis was made on the basis of edema and congestion of serosa, muscle and mucosa, associated with numerous wandering cells, round cell infiltration and the predominance of eosinophil cells (Fig. 1).

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*Case 2.*—A man, aged twenty-seven, was originally hospitalized because of nausea, hematemesis and melena. A diagnosis of cirrhosis of the liver was made following radiological studies which demonstrated multiple space-filling lesions of the distal esophagus which were interpreted as esophageal varices. He was transferred to a general hospital, and subsequent x-ray studies revealed the same radiological deformity of the distal area of the esophagus (Fig. 2). However, the patient's history and laboratory studies did not support the previous diagnosis of cirrhosis of the liver.

Since there was a history of mild bronchial asthma since childhood, associated with a 6 per cent eosinophilia and a history of urticaria in his son, esophagoscopy was done and this examination revealed a prominence of the rugae in the distal one third of the esophagus, associated with a pale boggy mucous membrane. No polyps or varicosities were found, although in areas the rugae were almost polypoid in size and swelling. A mucosal biopsy was taken and subsequent histological studies revealed edema and a hypersecretory state of the glands, plus a moderate eosinophilia which was compatible with the reversible sequence in early allergy (Fig. 3).

Subsequent observations and clinical studies revealed progressive improvement of the radiological, pathological and esophageal appearance. The patient was asymptomatic from a gastrointestinal standpoint upon his discharge from the hospital.

*Case 3.*—A man, aged thirty-six, for many years had experienced episodes of diarrhea, averaging two to six foul smelling stools daily for three to five days. From

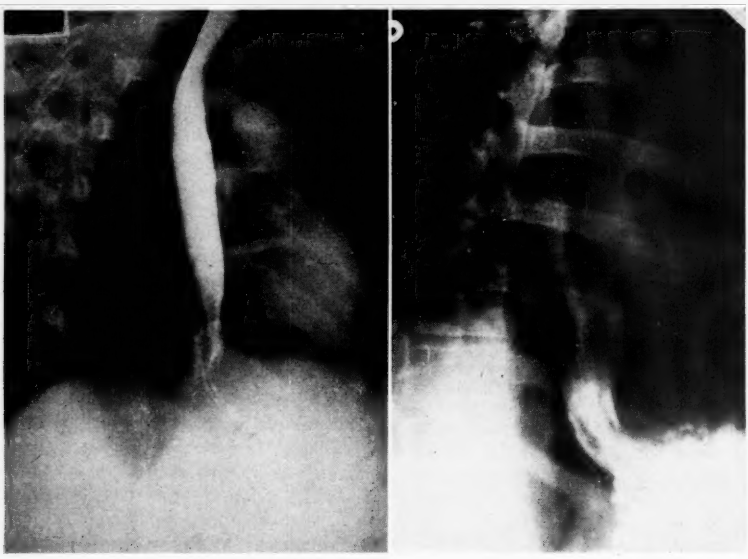

Fig. 2. *(Left)* Shows ragged moth eaten appearance of distal esophagus suggestive of varices. *(Right)* Reveals marked improvement.

the age of twelve to twenty he had repeated attacks of urticaria which ceased when he stopped eating tomatoes. In 1938, he began to experience summer episodes of mild attacks of wheezing and coughing. In 1940, he had a conjunctivitis for two weeks and later developed recurrent attacks of low back pain. In 1943, a tonsillectomy was done without benefit. He was hospitalized, and studies of foci of infection were done but no evidence of infection was found. Orthopedic studies were negative. Gastrointestinal examinations were normal except for a slight spasticity of the descending colon and a thrombosed internal hemorrhoid. A nose and throat examination revealed a bilateral allergic conjunctivitis and chronic allergic rhinitis. Laboratory studies were essentially negative.

Subsequent allergy studies revealed the following skin test reactions: marked reactions to pork, corn meal, white potatoes, tomatoes, coffee, cantaloupe, lemon, peach, pear and beef; moderate reactions to wheat, oats, carrot, lettuce, onion, dust and ragweed.

A diagnosis of constitutional allergy involving the respiratory and gastrointestinal system was made. The patient was placed on a diet and a multiple hyposensitization regime, with excellent results. He returned to duty. Numerous follow-up personal communications (J.R.) with him have revealed that he has continued his diet and injection therapy and that he has remained completely well.

*Case 4.*—A man, aged twenty-four, first experienced eczema on his neck and face at the age of ten when he lived on a dairy farm. This recurred and later became generalized, especially during cold weather. At sixteen years of age he experienced furunculosis during the winter. During his adolescence he began to develop recurrent gastrointestinal complaints, especially epigastric pain and constipation which was somewhat relieved by food or catharsis. Following his induction into the army, he

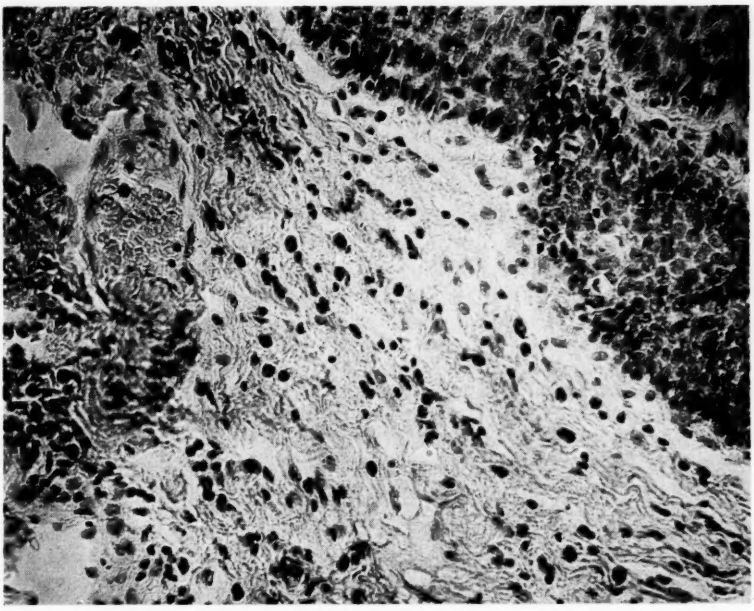

Fig. 3. Esophagus. Photomicrograph shows edema and round cell infiltration below lining epitholeum. Eosinophiles predominate in the exudate. The picture suggests allergic inflammation.

gained approximately 26 pounds. Eighteen months later, however, he began to lose weight and experienced headaches, dizzy spells, heartburn and water brash. A selective dyspepsia was also noted for onions, fried foods, cheese, bananas, fruit juice and tomato juice. Since his symptoms became progressively worse, he was hospitalized and observed as a possible case of gastritis. Gastrointestinal studies were negative, and an allergic survey revealed that he was markedly sensitive to milk, corn, cauliflower, potatoes, tomatoes, pineapple and walnuts. Following the institution of an allergen-free diet, he remained symptom free.

*Case 5.*—A man, aged thirty-two, had experienced episodes of headaches, postprandial fullness, epigastralgia, anorexia, nausea, pyrosis and occasionally vomiting since 1929. In 1935 he was hospitalized for one week and was told that he had a digestive dysfunction. His symptoms continued periodically, and no apparent relief resulted from any type of therapy. His symptoms became so severe that he was rehospitalized in 1943. Complete examinations were done and found to be negative. Allergic studies revealed that he was markedly sensitive to beef, veal, tuna fish, cabbage, tomato, pineapple and haddock. With the elimination of the above foods, this patient obtained almost instant relief, and by following this selective dietary regimen, he was able to return to duty.

## COMMENTS

At the present time there has been no satisfactory explanation of the physiopathological concept of selectivity in gastrointestinal allergy. Allergic conditions of the oral and anorectal area are more frequently noted, but

then they are more readily accessible in routine examinations. Allergic appendicitis has been demonstrated on several occasions, but as a clinical diagnosis it is rarely made. The writers believe that the presence of gastrointestinal allergy will be demonstrated more frequently in the future, especially when the impression of a good clinical history is verified by detailed endoscopic or tissue studies. Esophageal allergy is not common but should always be considered as a possibility in patients who present abnormalities in this area which are not readily explainable and, particularly so, when such individuals have a history of other allergic manifestations.

The treatment of these conditions is not always satisfactory due to the difficulty of demonstrating the basic allergen, but a great many patients are helped considerably by desensitization and dietary regimen.

SUMMARY

Gastrointestinal allergy is a definite entity and cannot be disregarded as an etiology of dyspepsia or other allied complaints. It is much more common than suspected, and undoubtedly many of the so-called functional states or nervous dyspeptics may in reality be due to allergic factors.

A detailed history and thorough clinical studies, including an allergic survey, may be necessary in order to make a final diagnosis in many vague so-called functional disturbances. Treatment when possible should be directed to a hyposensitization and dietary regimen.

Cases of allergic appendicitis, esophagitis and multiple food allergies have been presented as clinical entities, although their symptomatology suggested other organic disease or functional states.

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# BALSAM AS A CAUSE OF CONTACT DERMATITIS IN A FLORIST

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THE following case report adds balsam to the list of plants known to cause contact dermatitis.

## CASE REPORT

Mr. P. H. E., aged 56, a florist was first seen on December 3, 1943, because of a pruritic dermatitis on his face, neck, ears and hands which had been present for two weeks. The eruption began on the neck and wrists and spread rapidly to all exposed skin areas with the exception of the palmar surfaces of the hands. It consisted of pinpoint vesicles, with slight scaling around the hairline and in the creases of the neck and wrists. In the creases there was also beginning lichenification. There was diffuse erythema throughout, and the itching was intense.

A similiar rash had appeared first in 1940, about November 20, lasting until January 10 of the following year, 1941; it had reappeared each year thereafter during the same period.

Although the itching was intense at night, especially in bed, the patient was convinced that the rash was caused by something in his flower shop. There were no new contacts in his home during the period of his symptoms.

For the past three seasons, the patient had been under the care of a dermatologist, who agreed that the condition was a contact dermatitis, probably from some plant. He had tried topical treatments of all sorts, intravenous calcium and x-ray, all to no avail.

The dermatitis recurred each year at the time the Christmas greens and decorations were brought into the patient's flower shop. These included painted grasses, pine and pine cones, cedar and balsams. The flowers the patient handled during this period were roses and chrysanthemums, both of which were in his shop long before the appearance of the eruption. Knowing of the frequent occurrence of dermatitis from primroses, he never had had them in his shop. The patient thought his skin was worse when handling balsam, especially when he was breaking branches for sprays and wreaths. In 1943, the year he appeared for treatment, he refused to touch any balsams; nevertheless the rash appeared as before.

The present history of the patient was negative for other forms of allergy, but as a child, he had had a severe eczema of the face, neck and scalp.

The family history was negative for allergy as far as he could recall.

Arrangements were made for patch tests. Branches of balsam, pine and cedar were sent from the shop. An oil extract of each was prepared according to the technique of Shelmire and Black.[2]

Before the patient returned for application of the patch tests, he became ill with the then current grippe infection and was home in bed for three days. During that time the rash disappeared completely, but recurred twenty-four hours after his return to the shop.

On December 17 patch tests were applied for balsam, cedar, dog hair, wool, chrysanthemum. When the tests were removed twenty-four hours later, all were negative except the one for balsam. At this site there was a vesicular reaction about half the size of a dime, recorded as 2-plus. Two days later, the site of this test, which was on his back just below the collar line, had enlarged to the size of

*Read before the Chicago Society of Allergy, April, 1945.

a silver dollar and coalesced with the rash on the neck, which had become intensified in this area.

The treatment decided upon was oral desensitization. The oil extract of balsam was diluted 1:100 in Mazola according to Shelmire's directions,[1] and the patient was directed to take one drop in milk or fruit juice daily for three days, then increase one drop a day to maximum of five drops. He was also given Lowilla Cream (Westwood Pharmacal Company, Buffalo) to use as a protective coating when in his shop.

He was asked to report immediately after Christmas, but nothing was heard from him until January 15. The extract had been used as directed until the maximum dose of five drops had been taken for three days. Then he had stopped the treatment because the dermatitis seemed worse, but had resumed it after a week. He had taken a series of doses daily for several days, three different times, and each time he thought the eruption had been accentuated. This was considered a good indication that the extract was potent and specific, but that the dosage was incorrect.

The only local applications used were Lowilla Cream with a bland cold cream base. This proved very helpful as a protective coating, but was in no way curative.

He was advised to return the following fall to receive directions for preseasonal treatment, but in November, 1944, he was hospitalized for a cholecystectomy. He returned to his florist shop ten days before Christmas. Having some of the balsam extract in oil left from the preceding season, he started oral therapy at once according to the original directions. He took one drop a day for three days, increased a drop a day to a maximum of five drops, and then stopped. No rash appeared.

It is true that the period of exposure was shorter than usual and the intensity of the exposure somewhat less, because being convalescent, the patient spent most of his time in the office of his shop which was enclosed on three sides. However, he was in and out of the shop itself as well as the workroom where the wreaths and sprays were made. At no time during that season did he have any dermatitis, whereas in other years it had been present constantly from late November until the middle of January.

Before the next Christmas season, 1945-46, the patient had partially retired from his business and made it a point to keep out of the shop when balsam was on hand. Further testing of the oral desensitization was, therefore, not possible.

SUMMARY

A case of contact dermatitis due to balsam is reported. Oral desensitization with an oil extract of balsam was attempted.

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# AN EVALUATION OF ANTISTINE, A NEW ANTIHISTAMINIC SUBSTANCE

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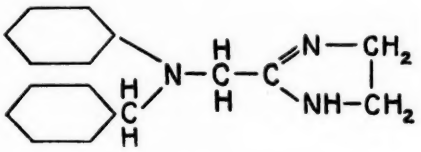
ANTISTINE is a new synthetic antihistamine substance with the following structural formula:



2-(N-phenyl-N-benzyl-aminomethyl) imidazolin

Animal experiments reveal that the drug has a relatively low toxicity, and exhibits both antihistamine and antianaphylactic action in the intact animal and isolated muscle preparation.[7] Reports in the European literature concerning the use of this new substance in certain allergic conditions have been favorable enough to warrant further investigation of both its antihistaminic and antiallergic actions.[2,9]

TABLE I. PROTECTIVE EFFECT OF ANTISTINE AGAINST HISTAMINE IN THE GUINEA PIG

| Antistine mg./kg. | Histamine mg./kg. | Number of Animals Injected | Mortality Per Cent |
|---|---|---|---|
| Control | 0.4 | 10 | 100 |
| 3 | 0.4 | 10 | 30 |
| 6 | 0.4 | 10 | 20 |
| 10 | 0.4 | 10 | 0 |
| 3 | 0.8 | 10 | 100 |
| 6 | 0.8 | 10 | 100 |
| 10 | 0.8 | 10 | 40 |
| 15 | 0.8 | 10 | 0 |

## ANTIHISTAMINE ACTION IN THE GUINEA PIG

Male guinea pigs, 300 to 450 grams in weight, were injected intraperitoneally with 3 to 15 mg. per kg. of Antistine* 15 minutes prior to the intravenous injection of varying doses of histamine† (Table II). The 100 per cent lethal dose by this technique is 0.4 mg. per kg. of histamine base.[5] Significant protection against this fatal dose was observed when 3 to 6 mg. per kg. of antistine was administered to each animal prior to

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*Antistine was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.
†Histamine Phosphate was furnished by Burroughs Wellcome and Co., (U.S.A.) Inc.

the injection of histamine, while 10 mg. per kg. of the drug protected all guinea pigs against this amount. When two lethal doses (0.8 mg. per kg.) of histamine were administered, 15 mg. per kg. of Antistine was required to protect all guinea pigs against fatal shock. A comparison with other antihistamine drugs tested in this manner reveals a smaller degree of protection against histamine on the part of Antistine as compared to Benadryl, Pyribenzamine, Antergan, and Neoantergan[6] (Table II).

TABLE II. COMPARATIVE ANTIHISTAMINE ACTIVITY IN THE GUINEA PIG

| 3 mg./kg. of Protective Drug | Number of Lethal Doses of Histamine Necessary to Produce 100% Mortality |
|---|---|
| Antistine | 2 |
| Benadryl | 5 |
| Antergan | 6 |
| Pyribenzamine | 37 |
| Neo-antergan | 124 |

TABLE III. CLINICAL RESULTS WITH ANTISTINE

| Condition Treated | Number of Cases | Helped | | Not Helped | |
|---|---|---|---|---|---|
| | | Number | Per Cent | Number | Per Cent |
| Bronchial Asthma | 24 | 9 | 37.50 | 15 | 62.50 |
| Vasomotor Rhinitis | 59 | 35 | 59.32 | 24 | 40.68 |
| Urticaria: | | | | | |
| Acute | 10 | 7 | 70.0 | 3 | 30.0 |
| Chronic | 9 | 3 | 33.34 | 6 | 66.66 |
| Penicillin | 1 | 0 | 0.0 | 1 | 100.0 |
| Allergic Headache | 6 | 1 | 16.67 | 5 | 83.33 |
| Atopic Dermatitis | 5 | 3 | 60.0 | 2 | 40.0 |
| Contact Dermatitis | 6 | 3 | 50.0 | 3 | 50.0 |
| Unclassified Dermatitis | 2 | 0 | 0.0 | 2 | 100.0 |
| Pruritis Ani | 1 | 0 | 0.0 | 1 | 100.0 |

## CLINICAL EVALUATION

Antistine was employed in 100 patients with one or more allergic complaints (Table III). Where effective, the drug produced symptomatic relief for periods of two to twelve hours, similar in nature to that exerted by other antihistamine drugs.[3] The degree of palliative action experienced, varied from patient to patient and frequently differed in the same patient from time to time. Successful action was recorded when appreciable amelioration of symptoms was noted following the use of the drug, and difficulty recurred upon withdrawal.

Fifty to 100 mg. four times daily, following meals and at bedtime, were prescribed in the average case, although considerable variation occurred depending on the needs of the individual patient. Doses of 50 mg. were first prescribed, and increased to 100 mg. after twenty-four hours if a beneficial action did not occur and no side effects were produced by the lower dosage. Where symptoms were more intensive, the

drug was administered every two to four hours. In children, doses of 50 mg. four times daily were tolerated without difficulty.

Antistine produced some degree of symptomatic relief in 59 per cent of patients with allergic rhinitis. The effect on rhinorrhea and sneezing appeared to be greater than on nasal blocking. Symptomatic improvement was observed in 37 per cent of asthmatic patients. In these cases, the drug usually benefited the cough to a greater degree than the dyspnea. Seven patients with asthma and associated rhinitis obtained appreciable relief of nasal symptoms, despite failure to affect the asthma. Greater action was apparent in acute than in chronic urticaria, 70 per cent of the former group being benefited, while only 33 per cent of the patients with the chronic type were improved. In one case of severe penicillin "serum sickness" type reaction, Antistine failed to relieve the symptoms. The pruritis accompanying 60 per cent of the cases of atopic eczema and 50 per cent of those with contact dermatitis was benefited by the drug, while the itching associated with two cases of unclassified dermatitis and one case of pruritis ani of allergic origin was not appreciably helped. Only one of six patients with periodic allergic headache was helped by 100 mg. doses of Antistine.

### CLINICAL COMPARISON WITH PYRIBENZAMINE

It was possible in many instances to make a clinical comparison between the effectiveness of Antistine and Pyribenzamine in the same individual (Table IV). While it is usually necessary in an evaluation of this type to rely on the patient's own impression as to the relative value of various medicaments, a more objective estimation is sometimes possible. In the present comparison, both drugs were at times prepared in capsule form and alternated without the knowledge of the patient. Placebo capsules were also used in eliminating as far as possible the psychologic factors involved in drug administration.

In fifty-one cases of rhinitis there were fourteen patients whose symptoms were helped only by Pyribenzamine. Eight others found that Antistine was the drug which afforded them symptomatic relief. Twenty-four patients (47 per cent of the total number) obtained some help from either drug. Upon further analysis of the latter group, it was found that ten patients obtained a relatively greater degree of action from Pyribenzamine, as compared to only four patients who found Antistine the more effective drug. Of the total number of fifty-one cases complaining of nasal symptoms, only five patients (9.8 per cent) failed to obtain some benefit from either drug.

The effectiveness of both drugs in asthma was relatively low, thoug' there were again some patients who were helped by one compound and not by the other. Pyribenzamine was usually more beneficial in urticaria. In only one case of this type was Antistine found more helpful. Pyribenza-

TABLE IV. COMPARISON OF ANTISTINE AND PYRIBENZAMINE IN THE SAME PATIENT

| Condition Treated | Number of Cases Receiving Both Drugs | Helped by Antistine But Not by PBZ | | Helped by PBZ But Not by Antistine | | Helped By Either Drug | | | | | | | | Total Receiving No Help From Either Drug | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | | PBZ Better | | Antistine Better | | No Difference | | | |
| | | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| Bronchial Asthma | 17 | 3 | 17.65 | 3 | 17.65 | 2 | 11.76 | 1 | 5.88 | 0 | 0.0 | 1 | 5.88 | 9 | 52.94 |
| Vasomotor Rhinitis | 51 | 8 | 15.69 | 14 | 27.45 | 24 | 47.06 | 10 | 19.61 | 4 | 7.84 | 10 | 19.61 | 5 | 9.80 |
| Urticaria: | | | | | | | | | | | | | | | |
| Acute | 5 | 1 | 7.69 | 1 | 7.69 | 3 | 23.07 | 2 | 15.38 | 0 | 0.0 | 1 | 7.69 | 0 | 0.0 |
| Chronic | 7 13 | 0 | 0.0 | 4 | 30.77 | 2 | 15.38 | 1 | 7.69 | 0 | 0.0 | 1 | 7.69 | 1 | 7.69 |
| Penicillin | 1 | 0 | 0.0 | 1 | 7.69 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Allergic Headache | 5 | 0 | 0.0 | 1 | 20.00 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 80.0 |
| Atopic Dermatitis | 1 | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Contact Dermatitis | 4 | 1 | 25.0 | 2 | 50.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 25.0 |
| Unclassified Dermatitis | 2 | 0 | 0.0 | 1 | 50.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 50.0 |
| Pruritis Ani | 1 | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

mine appeared to be slightly more effective in relieving the distress accompanying pruritic skin conditions. The majority of patients with headache of allergic origin failed to obtain relief from either compound.

TABLE V. SIDE EFFECTS WITH ANTISTINE

| | |
|---|---|
| Gastrointestinal Upset | 8 |
| Drowsiness | 7 |
| Vertigo | 3 |
| Dryness of Mucous Membranes | 2 |
| Fatigue | 1 |
| Palpitation | 1 |
| Dermatitis | 1 |
| Diplopia | 1 |
| Nervousness | 1 |
| Syncopy | 1 |

TABLE VI. COMPARATIVE SIDE EFFECT IN 72 PATIENTS RECEIVING ANTISTINE AND PYRIBENZAMINE

| | Number of Patients | Per Cent |
|---|---|---|
| Side effects from Antistine | 13 | 18.05 |
| Side effects from Pyribenzamine | 28 | 38.8 |
| Patients with side effects from Antistine able to tolerate PBZ without symptoms | 3 | |
| Patients with side effects from PBZ able to tolerate Antistine without symptoms. | 18 | |

### TOXICITY COMPARISON OF ANTISTINE AND PYRIBENZAMINE

Twenty-three per cent of those receiving Antistine experienced one or more side effects from doses of 100 mg. Gastrointestinal symptoms and drowsiness were most commonly encountered, but rarely necessitated discontinuing the drug (Table V).

In a group of seventy-two patients who received both drugs, the incidence of side effects from Antistine was 18.05 per cent, as compared to 38.8 per cent from Pyribenzamine (Table VI). Of the twenty-eight patients who experienced unpleasant reactions from Pyribenzamine, eighteen were able to take an effective dose of Antistine (50 to 100 mg.) without difficulty. The remaining ten individuals experienced essentially the same reaction from either drug. On the other hand, only three out of thirteen patients noting side effects from Antistine were able to tolerate a 50 mg. dose of Pyribenzamine.

### LOCAL USE OF ANTISTINE IN ALLERGIC EYE CONDITIONS

Experimental studies with antihistaminic agents in the past has suggested that failure to produce symptomatic effect in certain cases of allergy may be due to insufficient drug reaching the site of action.[4] The topical use of these substances on mucous membranes has been limited to a great

extent by the irritating properties of otherwise effective concentrations. On the basis of a report by Bourquin,[1] a 0.5 per cent solution of Antistine was employed locally in eleven cases of allergic conjunctivitis. Five patients reported a temporary smarting of the eyes following instillation of the solution. This disappeared within a few minutes, and in only one case was considered severe enough to stop the use of the drug. All but three patients experienced beneficial symptomatic action following the instillation of 1 or 2 drops into each eye, which lasted several hours. One patient reported aggravation of the eye condition by its use, while a second in whom the 0.5 per cent solution was too irritating, experienced a beneficial effect from a 0.25 per cent concentration of the drug. The drops were prescribed as necessary, and in some cases were used as often as every two hours for palliative effect. It appears that this solution offers some promise in the symptomatic treatment of certain cases of allergic conjunctivitis.

## DISCUSSION

The antihistaminic activity of Antistine as determined in the intact guinea pig is less than 10 per cent of that exhibited by Pyribenzamine. Yet a comparison of clinical activity in allergic patients does not reveal this wide variation. In the average individual a 50 mg. dose of Pyribenzamine appears to have the clinical effectiveness of a 100 mg. dose of Antistine. On the other hand, there are some patients who obtain greater benefi from Antistine even in equivalent doses. This apparent discrepancy in antihistamine effect and clinical action is similar to the lack of correlation determined for several drugs in histamine and anaphylactic shock.[8] It has been observed that while wide variations in the ability of these drugs to counteract histamine shock in the guinea pig exists, a similar difference in protective ability against anaphylaxis is not present. This suggests that histamine may play only a partial role in both the anaphylactic and allergic reactions, and that drugs with increasingly higher antihistamine action, as determined experimentally, will have no greater clinical effect than others of lesser potency. If this is true, the more promising developments in antihistamine therapy will come with the discovery of drugs which are better tolerated by the average patient. In the case of Antistine, an important factor which entitles it to a place in the growing list of useful antihistamine agents is its relatively low toxicity at effective dosage. It is also seen from the comparative study of Antistine and Pyribenzamine in the group of rhinitis patients that a trial of both drugs increased the total percentage obtaining symptomatic relief to 91.2 per cent. This would indicate that where symptoms fail to be affected by one antihistaminic agent, a favorable action may be obtained from the use of another of this series of compounds. It should again be emphasized, however, that Antistine as well as other antihistamine substances are palliative drugs, and no

lasting benefit should be expected from their use. Immunologic investigation and management is still a vital part of proper therapy in allergic disease.

SUMMARY

1. Antistine is a new synthetic antihistamine substance with the formul: 2-(N-phenyl-N-benzyl-aminomethyl) imidazolin. Ten mg. per kg. of Antistine was found to protect guinea pigs against one lethal dose of intravenous histamine, while 15 mg. per kg. prevented fatal shock when two lethal doses were administered.

2. Antistine in 50 to 100 mg. doses afforded symptomatic relief in the majority of cases of allergic rhinitis and urticaria. Less benefit was apparent in asthma, atopic dermatitis, contact eczema and allergic headache. A comparison between the action of Antistine and Pyribenzamine in the same patient indicated a greater effect on the part of Pyribenzamine in most instances. A smaller percentage found Antistine superior.

3. A 0.5 per cent solution of Antistine used in the eye produced symptomatic relief of burning and itching in cases of allergic conjunctivitis.

4. Side effects from Antistine were generally less frequent than with Pyribenzamine. In a group of patients in whom the two drugs were compared, it was found in many instances that those unable to tolerate Pyribenzamine could take Antistine in effective dosage without side effect.

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# OBSERVATIONS ON VARIATIONS IN REACTIVITY IN A CASE OF ALLERGY TO PENICILLIN

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ALLERGIC reactions to penicillin have now become well known. Such manifestations of hypersensitivity as dermatitis,[1] asthma,[6] anaphylactic shock,[8] the Arthus phenomenon[7] and the like have all been described following its administration. Kalodny and Denhoff,[4] however, found even in a group of consistent reactors to penicillin "that a phase of relative anergy existed for a period of five to seven days" and noted that skin tests were not consistently positive. Zeller[9] has reported a case which well illustrates the variations in the degree of sensitivity. He points out that as little as 50 units of commercial penicillin sodium will produce urticaria during the reactive phase, but during the anergic state, in his case, the week following the cessation of symptoms, increasing doses of penicillin up to 25,000 units produced no reaction of hypersensitivity. The present case is described because of the variations in reactivity observed and the advantage taken from these observations for therapeutic action.

## CASE REPORT

I. H., a fifty-nine-year-old white woman, was admitted to the Medical Service of the Cincinnati General Hospital, May 1, 1946, because of hypertensive arteriosclerotic heart disease complicated by a large carbuncle of the hip. Penicillin therapy, in dosages of 50,000 units intramuscularly every three hours, was instituted on the day of admission. On the second day of penicillin therapy her temperature rose to 103° F. There was intense redness and edema around each site of injection. A generalized, maculo-papular erythematous eruption was noted, which was most intense over the flexures of the elbows, axillae, and groin. Penicillin injections were stopped. The rash receded and the temperature returned to normal within the succeeding twenty-four hours. The carbuncle was then incised and drained. Two days later 50,000 units of penicillin were given orally every two hours for one day, which did not reproduce the rash. The patient, however, complained of soreness and tenderness of the tongue and mouth. Examination showed the tongue and buccal mucosa to be red and slightly edematous. Penicillin was stopped. The patient improved and was discharged from the hospital May 5, 1946. No skin tests had been done.

The patient was readmitted to the hospital on August 25, 1946, with an acute keratoconjunctivitis. The right eye showed marked edema of the lids and some erythema. The bulbar and palpebral conjunctivae were red and showed cilliary injection. Chemosis was marked. There was a hazy opaque grayish-white infiltration and ulceration about the entire limbus extending across the pupillary area. The aqueous humor appeared to be clear, and the iris was normal in color. The pupil was 3 mm. in diameter, round, nonreactive to light. The red reflex was obtained from the fundus, but due to the corneal haziness no fundoscopic details could be distinguished. The tension was normal to palpation, but the patient was unable to distinguish form. There was some photophobia.

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A pneumococcus, type VII, was isolated in pure culture from the right eye. This organism was assayed as sensitive to less than 0.03 units of penicillin per c.c. It was therefore thought desirable that penicillin therapy be given. Because of her history of hypersensitivity reactions on her previous admission, the institution of therapy was preceded by cutaneous tests to penicillin. A patch test with 200 units of amorphous commercial penicillin was placed on the right upper arm; both an intradermal and scratch test with 200 units of the same penicillin was done on the left forearm. All of these tests were entirely negative both in twenty minutes and in forty-eight hours.

Penicillin, in dosages of 50,000 units intramuscularly every three hours with amorphous commercial penicillin, was started on August 27, 1946. Atropine sulfate drops were used locally. There was no untoward reaction until after five days of penicillin therapy when a generalized erythema was noted. Twenty-four hours later a typical erythematous, generalized, maculopapular dermatitis appeared, almost explosively. Pruritus was intense and the rash most marked in the axillae, groins, and flexures of the elbows. At this time the patient's eye had shown much improvement. Penicillin therapy was discontinued, but not the treatment with atropine sulfate drops. A solution of sulfathiazole was also instilled into the affected eye. At the end of forty-eight hours the pruritus, erythema and rash had almost entirely receded.

A patch test with 200 units of crystalline penicillin G was done on the right upper arm. It was negative at the end of forty eight hours. An intradermal test with 2.5 units of crystalline penicillin G dissolved in 0.1 c.c. of normal saline produced an immediate erythema and edema with accentuation of the original injection wheal. There was a slightly elevated central edema; spreading pseudopodia appeared within twenty minutes and then receded in approximately one hour; an accentuation of this raction was noted again in approximately six hours and persisted as a tuberculin-type reaction for the succeeding forty-eight hours. A control intradermal test with normal saline 0.1 c.c. was negative.

At the end of this time, the patient had an exacerbation of the keratoconjunctivitis, to which the response with topical sulfathiazole was unsatisfactory. Penicillin therapy was therefore resumed cautiously in the form of topical application of a solution containing 500 units per c.c. of amorphous penicillin in normal saline. This was instilled into the affected eye every three hours, and improvement followed for forty-eight hours. At that time, erythema, edema and vesiculation were noted on the periorbital region of the affected eye, over the cheek and extending to the areas of the face that had come in contact with the penicillin solution. A patch test on the arm was negative, but a patch test with 200 units of amorphous commercial penicillin on the angle of the right jaw gave a 2-plus reaction in twenty-four hours. A patch test of the left side of the face with the atropine eye drops was negative in twenty-four hours and remained so for the succeeding forty-eight hours. An intradermal test with sulfathiazole by Leftwich's method[5] was negative; patch testing of the upper arm and left face with sulfathiazole powder was negative. A repeated intradermal test with 200 units of amorphous commercial penicillin on the right forearm gave no immediate reaction and was negative at the end of forty-eight hours.

Two days later, a repeated patch test with 200 units of amorphous penicillin to the right face was negative at the end of forty-eight hours. At this stage of her illness an incidental coronary occlusion occurred. We felt that the results of the skin tests indicated a state of anergy to penicillin. Faced by the alternative of enucleation of the diseased eye under the handicap of her cardiac condition, it was decided to chance a resumption of penicillin therapy, which was given intramuscularly in dosages of 50,000 units of amorphous penicillin every three hours. The antibiotic was tolerated well for seven days, and resulted in rapid improvement in her eye condition. After several weeks of bed rest because of her coronary occulsion, she was discharged from the hospital free from symptoms of disease September 21, 1946.

A repeated intradermal test with 2.5 units of amorphous penicillin, using the same brand and lot that was used for her last course of therapy, thirty-one days after discharge gave an immediate reaginogenic type of reaction as well as a tuberculin-type reaction at the end of forty-eight hours. Repeated patch test with 200 units of the same amorphous penicillin gave a 2-plus reaction in forty-eight hours. Contact testing of the buccal mucous membrane[2,3] with 200 units of crystalline penicillin G showed a moderately positive reaction after one hour of contact. This persisted for twenty-four hours. Control contact tests were negative.

## CONCLUSIONS

1. Patients under prolonged or repeated observation may show wide variations in the degree of hypersensitivity to penicillin.

2. The correlation of hypersensitivity reaction, cutaneous testing and penicillin therapy may be demonstrated.

3. Advantage may be taken from the demonstration of periods of relative anergy to penicillin for therapeutic action. It is obvious that the unavoidable risk involved will justify such procedure only in grave emergencies.

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## DR. MORRIS FISHBEIN TO GIVE COURSE IN MEDICAL WRITING

Dr. Morris Fishbein, Editor of the J.A.M.A., will give an instructional course in medical writing at the next annual meeting of the Mississippi Valley Medical Editors' Association, to be held at Springfield, Illinois, next September 29 during the annual meeting of the Mississippi Valley Medical Society in that city. No registration fee will be charged to members of the Association.

The Medical Editors' Association is contemplating changes in both its constitution and name, as it is felt that the name "Editors" is entirely too restrictive, and the name Medical "Writers" or "Authors" Association would be more appropriate. While every medical editor is a medical writer, every medical writer is not a medical editor. Since the principal purpose of the Association is to improve medical writing, hundreds of physicians should be interested in the organization, as most progressive physicians write articles and are interested in any effort to improve medical literature.

All interested in knowing more about this non-profit organization, or attending the meeting next September, should communicate with the Secretary, Dr. Harold Swanberg, 209-224 W.C.U. Bldg., Quincy, Illinois.

# ALLERGY IN CHILDREN AS RELATED TO ALTITUDE

JULIA BAKER, M.D.
Mexico City, Mexico

CERTAIN observations during the last seven years on children in Mexico City have led to the conviction that altitude *per se* plays a part in the initiation and severity of allergic reactions. The conclusion seems inescapable that allergic tendencies are unduly common and severe at the high altitude of Mexico City (7,325 feet) and appear frequently in children never noticeably afflicted with allergic tendencies at lower altitudes. The evidence is based on the study of a random sample of 500 children in Mexico City which gave allergic symptoms in 48 per cent. This supplements a previous random sample of 500 which gave allergic symptoms in 53 per cent.[1] Of the 1,000 there were 509 who had allergic symptoms. The study includes sixty-two children who lived part of the time in Mexico City and part of the time at lower altitudes and who showed more allergic symptoms while in Mexico City. Two of these cases have been previously discussed.[2] Charts on seven others are included in this paper. Experimental evidence on the effect of altitude on anaphylactic shock has been previously cited.[1]

That the conditions observed and here referred to are allergic manifestations is supported by the following evidence: (1) Symptoms of children previously proved in the U. S. to be allergic become much worse at the altitude of Mexico City. (2) Children with allergic family history or allergic siblings have shown more allergic symptoms in Mexico City than at lower altitudes. (3) Symptoms are definitely related to the ingestion of certain foods and abate when these foods are omitted from the diet. (4) The foods most commonly causing the reactions are eggs, milk, orange juice, chocolate and wheat, foods recorded as causing allergic reactions in the U. S. (5) The reactions are not a result of the character of the food in Mexico City since the symptoms are commonly related to ingestion of different brands of powdered and canned milk imported from the U. S., as well as imported chocolate, soy bean milk, et cetera. (6) That the reactions have not been the result of infections has been established by blood counts, stool examinations, cultures, et cetera. (7) The symptoms involve the skin, the gastrointestinal tract and the respiratory tract, as usually defined in allergic cases. (8) Reactions to altitudes are not affected by race. Of 140 Mexican children in the group of 500, seventy-two were allergic (50.1 per cent). The other 360 children were Americans, with a few Europeans. Of the group of 203 younger children from six months to five years of age, seventy were Mexican. Of these seventy Mexican children, thirty-seven had hives (50.3 per cent).

Presented at the Third Annual Meeting of the American College of Allergists at Atlantic City, N. J., June, 1947.

SYMPTOMS

*Skin.*—Hives are the most common and clear-cut symptom. They appear as red macules about 1 to 1.5 cm. in diameter with irregular outline, itch intensely, and often form small vesicles about 2 mm. in diameter. If scratched, scabs form and there may follow a pigmented scar lasting several weeks. They are usually located on the trunk but may also be present on the face and extremities. They occur in crops and are usually accompanied by gastrointestinal or respiratory symptoms. They are distinguished from insect bites occurring in Mexico City by their character and by history. Generalized urticaria, as distinguished from what I refer to as hives, and atopic dermatitis occur commonly but less frequently than hives.

*Gastrointestinal Symptoms.*—These are anorexia, nausea, vomiting, abdominal pain, loose and frequent evacuations. If these symptoms are definitely related on three occasions to the ingestion of certain foods and abate when these foods are omitted from the diet, if the symptoms are also accompanied by hives, and if the blood-count is not elevated, the case is recorded as allergic. If any aspect suggests a doubt, stool examinations and cultures are done.

*Respiratory Symptoms.*—These symptoms consist of asthma, rhinitis with pale mucous membrane and watery discharge lasting more than a week, and in some cases chronic cough with postnasal drip. Tuberculin tests and x-rays are done on these cases, and if the conditions clear up suddenly on removing certain foods or inhalants, or skin tests to inhalants are positive and these prove clinically to be the offenders, the cases are recorded as allergic.

The gastrointestinal symptoms and the respiratory symptoms require more careful study to establish them as allergic than do the skin manifestations. Since hives, generalized urticaria and atopic dermatitis are very common in the age group of six months to five years, and since these symptoms are sharply defined, I have selected from within this age group patients on whom the record is sufficiently long to establish any definite relation between diet and hives. There are 203 individuals thus selected from this age group. Of these, 104 (51 per cent) have had skin symptoms attributable to certain foods. In this group of 203 children, there were twelve cases of geographic tongue (5.9 per cent), and in the group of 500 children there were twenty-five cases (5 per cent).

The detail of some of these cases at high and low altitudes appears on the charts, arrangement of which is according to an article on "Charting and Symbols" by Dr. Abraham B. Schwartz, published in *Journal of Pediatrics,* October, 1946.

ALLERGY RELATED TO ALTITUDE—BAKER

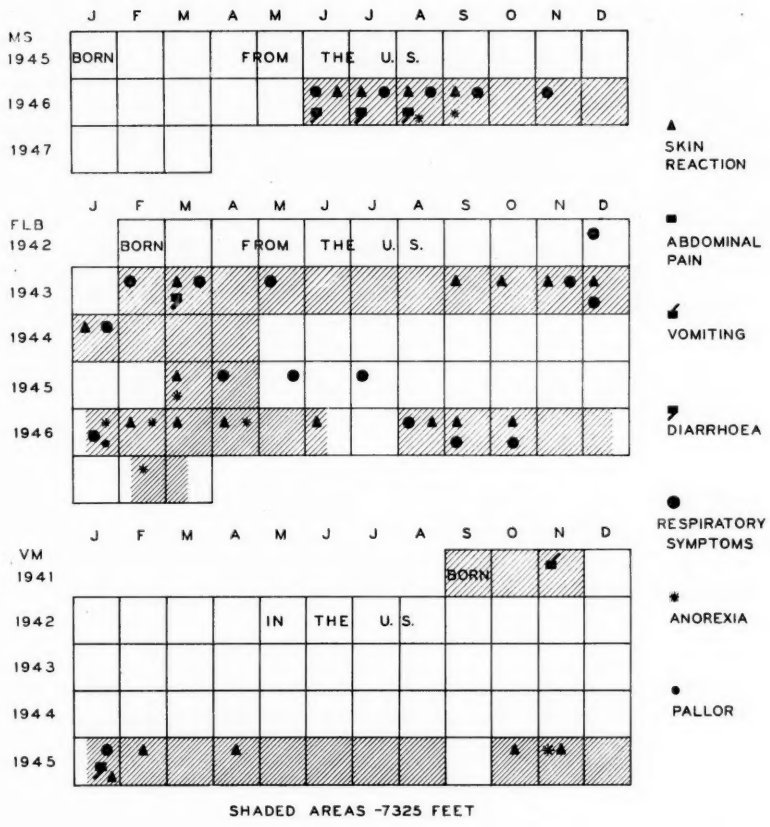


Chart I.

## DISCUSSION OF THE CHARTS

M.S. had never been ill before coming to Mexico. He had never had hives, colds, or loose bowel movements. He arrived in Mexico City in May, 1946, and immediately developed hives, loose bowel movements and running nose. All these lasted until July when he was first seen and put on a diet without milk, eggs or orange juice. His nose became better, bowel movements were reduced from five to two a day and no new hives appeared. On August 29 milk was given. He broke out in hives and his nose began to run, so milk was discontinued. On September 20 milk was begun again gradually, but he broke out in a rash. Milk was discontinued. October was uneventful. On November 8 he began to have a chronically running nose, but as skin and gastrointestinal tract were normal no further limitations were put on the diet. In December, 1946, he returned to Barberton, Ohio. A letter from his mother dated March 17, 1947, stated that he could eat everything including eggs, milk, and orange juice, and that he had no hives, rashes, running nose or loose bowel movements in the U. S. Another communication on May 20 stated that he was still symptom-free on a full diet.

F. L. B. had no allergic history and had been well from birth except for a respiratory infection in December, 1942. At the age of one year she arrived in Mexico City, on February 11, 1943. She developed a running nose, and in March, eczema. Eggs were recorded as disagreeing with her on several occasions. The eczema in March was accompanied by loose bowel movements and a running nose. With some dietary restrictions she became better and was free of skin symptoms until September when she developed hives. The hives recurred during October, November, December and January. In May, 1944, she went to the U. S. and stayed until March, 1945. On arrival in Mexico City, she developed generalized rash and anorexia, but improved on limiting the diet. In May, 1945, she went to the U. S. and stayed until January, 1946, where she was again free of symptoms. At this time she could eat chocolate with no ill effects, though if she ate it in Mexico City she developed hives. From January, 1946, through July she had hives frequently. In June and July, 1946, she spent six weeks in the U. S. and ate everything without reactions, but immediately on her return to Mexico City she developed hives and a running nose, both of which conditions lasted three months. On omitting wheat from the diet, these symptoms cleared up. On December 7, 1946, she went to the U. S. and stayed until February 7. While there she took eggs, milk, orange juice and wheat, and had no hives or running nose.

V. M. was born in Mexico City in September, 1941, and in November she began to vomit frequently. She went to Boston on December 1, 1941, and had no more vomiting. Her stay in the U. S. was prolonged and she had good health. Her mother asserts positively that she had no hives or gastrointestinal disturbances. She came to Mexico City in January, 1945, at the age of three and one-half years. On arrival she developed hives, loose bowel movements and running nose. The hives became severe in April, and were alleviated by reducing milk. She went to El Paso, Texas, for one month in September, 1945, and was very well, had an excellent appetite, and could eat eggs and drink orange juice there without getting hives. She cannot take eggs and orange juice in Mexico City. On returning to Mexico City in October, she broke out with hives and lost her appetite.

*Chart II*

C. S. arrived in Mexico City on April 30, 1946. He had been completely well during the sixteen months of his life. On arrival he developed hives, anorexia and three to six loose bowel movements a day. The bowel movements became normal on omitting milk. Powdered milk was later begun very gradually, but he developed loose bowel movements. The family returned to the U. S. on July 28, 1946, because the child could not tolerate milk in Mexico City.

B. J. F. was born in March, 1945, and lived in the U. S. until February, 1946, during which time she had a good appetite, clear skin, normal bowel movements and no illness of any kind. She arrived in Mexico City on February 1, 1946, and developed an atopic dermatitis on her cheeks, and anorexia. Omitting eggs and orange juice relieved the anorexia. In June, 1946, loose bowel movements were corrected by omitting milk from the diet. Later evaporated milk imported from the U. S. was begun gradually, but on October 4, 1946, she developed loose bowel movements, anorexia and extreme pallor. On omitting milk these symptoms disappeared. Milk was omitted from October 4 until November 7. During the month from November 7 to December 6, she took daily one cup of diluted evaporated milk imported from the U. S., and lost weight, so it was again omitted, and from December 6 to January 6, 1947, she gained weight.

C. F. was born in February, 1943, lived uneventfully in the U. S. with no hives or illness of any sort until arriving in Mexico City in December, 1944, whereupon he broke out in hives that lasted for three weeks. At the same time he developed

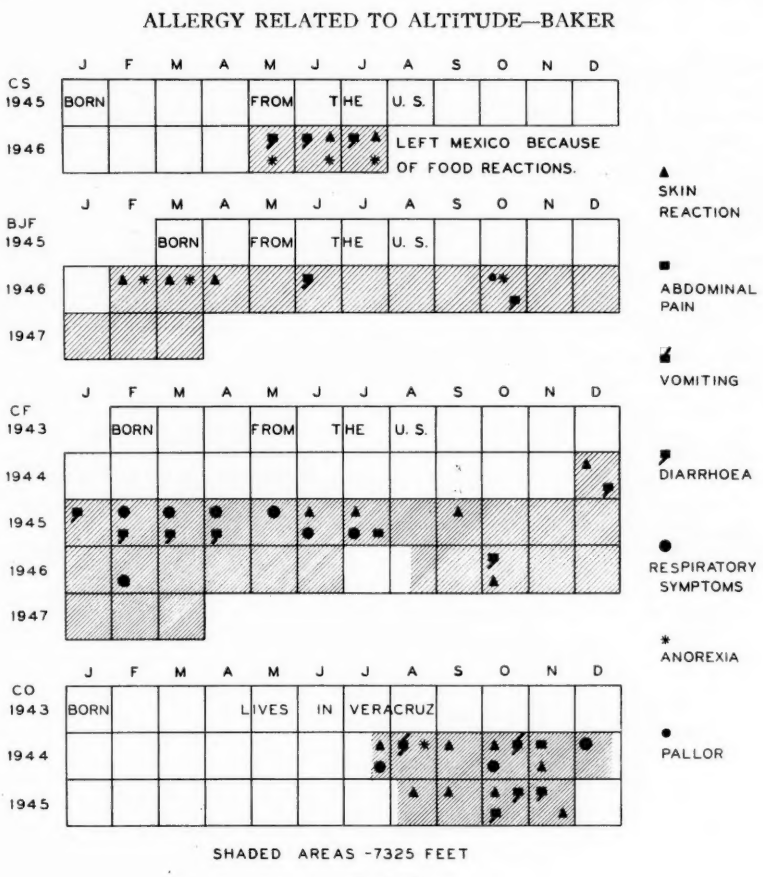


Chart II.

loose bowel movements, three to four a day, and this lasted through December, January, February, March, and April. During this same period, he developed a chronically running nose which lasted from February to July. When his diet was limited over short periods, improvement in the symptoms was noted, but this was done only sporadically, and for a short time following acute episodes. He went to the U. S. in July, 1946, and was very well, with improved appetite. On his return to Mexico City, he had no trouble until October when he developed hives and loose bowel movements, which were controlled by diet.

C. O. was born in January, 1943, and lived at sea level in Veracruz, Mexico. He came to Mexico City July 25, 1944. On August 4 he developed loose bowel movements, three times a day, and on August 7 began to vomit everything so that he became acidotic and had to have intravenous Hartman's solution. On a limited diet he improved. He was still getting milk, but this was omitted later, on December 15, because of constantly running nose. The condition improved with this limitation of diet. However, all during his five months' stay in Mexico City he had symptoms related to the gastrointestinal tract, the skin, and the respiratory system (as seen on the chart), although not so severe as on arrival. He was in Veracruz a year, where

he had no trouble, and returned to Mexico City in August, 1945. It was definitely recorded at this time that eggs and chocolate caused him to have loose bowel movements and hives in Mexico City but not in Veracruz. He had hives all during his stay in Mexico City in 1945. He was never known to have hives in Veracruz.

I shall discuss one more case although it does not appear on the charts. L. S. was born in the U. S. in April, 1943. Soon after birth she developed vomiting, a symptom evident for one year and assigned as allergic by her physician. Pablum, egg, apricot and apple caused vomiting and hives. At one year the vomiting stopped, but she had abdominal pain and gas, always relieved by enema and definitely related to certain foods. At two years she began to improve, and at two and a half years she could eat all foods. At two years and eight months she came to Mexico City. On a full diet she had minor allergic symptoms for two months, and in February, 1946, two months after arrival, she developed severe allergy with sneezing, running nose, severe abdominal pain, anorexia and hives. According to her mother, the time in Mexico City was the worst period of her life in regard to allergy, and her symptoms were kept under control only by a diet without milk, orange juice, egg, apricot and wheat. She went to West Point in April, 1946, and improved immediately. She was free from abdominal pain and began to gain weight. She was able to take milk and wheat without trouble, but a letter from her mother in January, 1947, stated that she was still unable to tolerate orange juice.

SUMMARY

Of 1,000 children seen in general pediatrics practice, 509 have shown definite allergic symptoms in Mexico City at an altitude of 7,325. Sixty-two children who lived part of the time in Mexico City and part of the time at lower altitudes were free of these allergic symptoms at the lower altitudes, or the symptoms were less severe there. Charts of seven of these cases are shown.

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# SYMPTOMATIC PURPURA OCCURRING WITH MALARIA

HAROLD G. NELSON, LT. (J.G.), MC, USNR
and
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OBSERVATIONS made on a male veteran of World War II during the course of his first clinically recognized attack of malaria are described herein. The significance of the report resides in the fact that approximately two weeks after the onset of an undiagnosed illness, characterized by chills and fever and later proved to be malaria, this man developed petechial hemorrhages in the conjunctiva of both eyes and in the mucous membrane covering the palate.

All of the textbook descriptions of malaria do not mention purpura as a manifestation of the disease. Shrager and Kean[5] found, however, in reviewing the literature on the subject, that various hemorrhagic manifestations (petechiae, ecchymosis, epistaxis, and hemoglobinuria) have been described. These were said to have occurred usually in early pernicious cases of malaria and occasionally in the chronic forms of the disease. They also reported ten new cases of purpura found among 10,000 consecutive patients with malaria seen at the Gorgas Hospital. Four of the patients were placed on the seriously ill list because of the purpura, and two died. Nine of the ten cases developed purpura following the administration of quinine, and it is perhaps not unreasonable to assume that this played a role in the genesis of the condition. However, since the cases were not tested for sensitivity to quinine, and since various studies have suggested that malarial parasities and quinine in combination may occasionally produce such an effect, the exact etiology of the lesions observed in their cases remains in doubt.

Allergic manifestations other than purpura, considered due to the sensitivity of the human host to the infecting malarial organism, are likewise seldom seen, but do occur.[1]

Since reported instances of purpura associated with malaria are rare, and since the clinical finding could readily lead to an erroneous diagnosis of bacteremia, a report seems appropriate.

## CASE REPORT

A thirty-year-old veteran (J.F.J.), employed as a butcher, was admitted to the hospital on December 26, 1946, complaining of recurrent "fever and chills". The attacks had begun about two weeks prior to admission and had occurred practically every other day. They were usually accompanied by severe headache, backache, and pains in the muscles and joints. During the intervals between the

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(The opinions set forth in this article are those of the writers and are not to be construed as necessarily reflecting the policies of the Navy Department.)

paroxysms the patient felt fairly well. Several days following the onset of his illness, he had consulted a physician who had prescribed sulfadiazine, 1 Gm. every four hours for four doses. One week before entering the hospital the patient had been given quinine sulfate, 5 gr. for three doses. Neither of these drugs had appreciably influenced his symptoms.

A review of the patient's past history revealed that in 1944 and 1945 he had been stationed in the Southwest Pacific on New Guinea and Leyte. He had taken suppressive dose of atabrine from the time he entered the above-mentioned areas until he returned to the United States in 1945, and did not develop clinical malaria prior to the onset of his present illness.

Physical examination at the time of admission revealed a well-developed, rather obese white man who appeared acutely ill. The temperature was 102° F. and the pulse rate was 134. The blood pressure was 100/74.There was no skin erythema. The eyes showed bilateral subconjunctival hemorrhages. There were a number of pinpoint hemorrhages present in the soft palate. There were no heart murmurs, and the lungs were clear to auscultation and percussion. The liver and spleen were not enlarged to palpation and percussion.

The admission diagnosis was "probable septicemia."

*Laboratory Findings.*—The red blood cell count was 4,800,000; the hemoglobin was 14.5 grams (Haden-Hausser), and the leukocyte count was 10,200. The differential count was 56 polymorphonuclear cells, 36 lymphocytes, 3 eosinophiles, 1 basophile and 4 monocytes. The bleeding time (Duke) was 4 minutes, and the clotting time was 2½ minutes. The platelet count was 264,000. The prothrombin time was 19 seconds (control—17 seconds). A thin blood smear was positive for Plasmodium vivax. Early ring forms and infected erythrocytes containing Schüffner's dots were observed in moderate numbers. The Kahn test was negative. The urinalysis was normal. Blood cultures using tryptose phosphate broth and Brewer's medium were negative at the end of two weeks.

*Treatment and Course.*—After the diagnosis of malaria was established, the patient was given atabrine, 3 gr. every six hours. Within twenty-four hours after the institution of therapy, the subconjunctival hemorrhages had begun to fade. The hemorrhages in the soft palate, however, showed no change. After a week the petechiae in the soft palate had disappeared; only faint traces of the subconjunctival hemorrhages remained, and the patient felt well except for some "nervousness."

In an attempt to determine the sensitivity of the patient to quinine, a scratch test using a 1:10 dilution of quinine sulfate was done seventeen days following the first ingestion of quinine. The reaction to this was negative. Feinberg[3] states that quinine is unlike many of the simple drugs, in that positive scratch reactions may occur in patients sensitive to this drug.

Three 5-grain capsules of quinine sulfate were given to the patient following the scratch test in an effort to determine whether this would elicit any allergic phenomena. Purpuric manifestations failed to develop following the ingestion of this drug.

The patient was also given 1 Gm. of sulfadiazine four times a day for two days to rule it out as a possible cause of the purpura. No purpura developed following the administration of sulfadiazine.

The patient was seen seven months after he left the hospital and had had no further purpuric manifestations.

## DISCUSSION

It has been shown[2] that urticaria is not uncommon following the administration of quinine. In this regard, the postulation of Quick[4] is interesting, in that he predicates that the release of histamine is the basic cause of both simple urticaria and thrombocytopenic purpura and the difference in the two is merely quantitative.

This case represents a patient who developed purpuric manifestations during an infection with Plasmodium vivax. The role of the quinine in the genesis of the purpura is not clear. However, the negative scratch test to quinine sulfate and the failure to develop purpuric manifestations following test doses of quinine indicate that the purpura was probably due to the malarial infection.

## SUMMARY

A case of malaria with symptomatic purpura is described. A partial review of the literature and a brief discussion of the significance of this manifestation are presented.

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# THE USE OF MICRONIZED THERAPEUTIC AGENTS BY INHALATION
## With Special Reference to Allergic Pulmonary Conditions

GEORGE V. TAPLIN, M.D., and FRED A. BRYAN, M.D.
Los Angeles, California

IN our preliminary report we described a method of administering by inhalation various finely divided, solid therapeutic agents suspended in air.

To an allergist, dusts have always meant trouble; however, dusts do have some properties which are quite interesting. It has been known for a considerable time that the particle size of various dusts plays a very important role in the toxicology of the dust. For example, dusts of silicon dioxide with particle sizes above 10 to 15 microns usually fail to reach the alveoli of the lung and thus do not play an important part as a causative factor of silicosis; however, particles ranging around 1 micron do reach the alveoli, and considerable numbers of them remain in the alveoli for a long enough period to produce the reactions noted in silicosis. Particles which are considerably finer than 1 micron have a tendency to be expelled from the alveoli and the respiratory tree with the exhaled breath. If a soluble compound is considered in the form of a dust, we feel that the most efficacious particle size for that dust to be absorbed from the lungs is approximately 1 micron. Therefore, we have produced our finely divided penicillin-glucose mixtures with a mean particle size range of 1 micron. Light microscope and electron microscope studies of the particle size distribution of our preparation show that the mean particle size ranges around 1 micron, greatest longitudinal dimension.

Administration of micronized therapeutic agents to animals by inhalation has been performed. Histological sections of the respiratory tract made at various intervals after administration have shown no abnormalities.

So far, the utilization of any solid dry therapeutic agent, which is not gummy or elastic in nature, has presented no difficulties in preparation for use by this method. It would be safe to say that the limiting factors in the use of any solid therapeutic agent by this method would be the absorbability by the respiratory tree and the pharmacological properties of the agent.

To maintain the potency of penicillin, it is necessary to keep the preparation dry. This also prevents agglomeration of the fine dust particles. Therefore, in the preparation of our materials we find that dryness and fine particle size are of utmost importance.

### THE APPARATUS

The equipment for producing the suspension of fine particles in air is comparatively simple, and on repeated tests has proven to be most

Dr. Taplin and Dr. Bryan are associate clinical professors of medicine at UCLA Medical School.
Work performed at the University of Rochester School of Medicine and Dentistry, in the Departments of Medicine and Radiology, under a grant-in-aid from the Lederle Laboratories Division of American Cyanamid Company.

efficient.[4] At present, there are two types of equipment, one consists of a 1-inch diameter plastic tube, approximately 4 inches long, which is divided into two chambers—an upper chamber where the finely divided

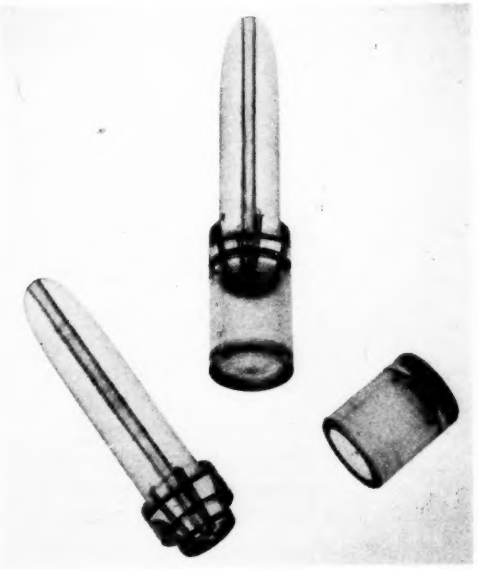

Fig. 1. *(left)* The large apparatus for administering micronized therapeutic agents.

Fig. 2. *(above)* The disposable apparatus.

therapeutic agent is placed, and a lower chamber which contains a dehydrating agent for drying the air to be passed over the therapeutic agent. This apparatus requires air pressure from a standard rubber bulb (Fig. 1).

The second piece of equipment is much smaller and does not require the use of a rubber bulb. It consists of a solid upper portion, approximately 2 inches long and shaped to fit either into a nostril or into the mouth. This portion contains the outlet vent and the inlet orifices for producing the air turbulence which in turn produces the suspension of the therapeutic agent. This apparatus is fitted with a small cup which attaches to the base. This cup acts as the container and also is an hermetically sealed dispenser of measured amounts of the therapeutic agent. Therefore, no dehydrating agent is necessary with his apparatus (Fig. 2).

In practice, the first piece of equipment described is used in the following manner: The top cap is unscrewed, and a capsule containing a measured

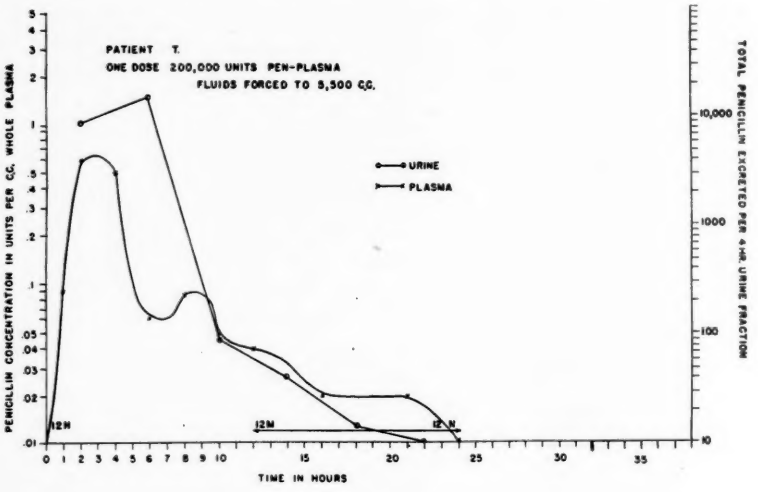


Fig. 3.

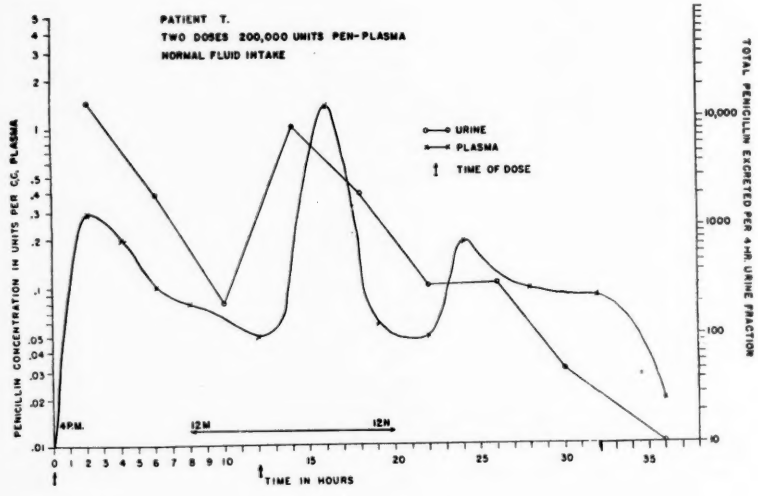


Fig. 4.

amount of the finely ground therapeutic agent or agents, either with or without a vehicle such as glucose, is emptied into the upper chamber. The cap is then replaced and the equipment held so that the outlet tube is slightly within the partially opened mouth. The patient first exhales deeply and then takes a slow, long inspiration. During the period of inspiration, the

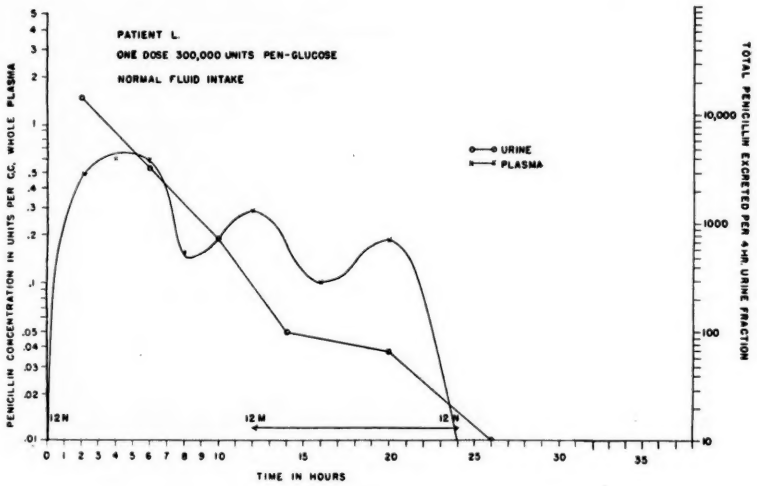


Fig. 5.

rubber bulb is compressed with rapid, light strokes. Heavy compression of the bulb produces a very dense suspension and might cause coughing. At the end of the period of inspiration, the patient stops compressing the bulb, holds the breath for a few seconds, then exhales through the nose and repeats the procedure until the therapeutic agent is entirely used—which takes approximately three minutes.

In the small disposable type of apparatus, the solid upper portion is held in the hand and the small cup-like container is uncapped and screwed onto the delivery tube portion. In some of our models, the cup is attached to the delivery tube portion by means of a press fit. The patient then exhales deeply, inserts the delivery tube either into the mouth or into one nostril, and then inspires slowly and deeply. This procedure is repeated until the therapeutic agent is completely gone from the cup. It is important that the patient does not exhale or blow back into the apparatus.

## PENICILLIN

The first agent studied was crystallin potassium penicillin. To prove its effectiveness by this route, it was necessary to determine its rate of absorption and excretion. At first this was done using protocols described by Segal et al[3] for aerosol penicillin. Soon it was found that the blood concentrations were higher and more sustained than those recorded after inhalation of mist type penicillin aerosols by several investigators. A serial dilution method of penicillin assay was used[2] and found cumbersome, tedious, and difficult to reduplicate. By modification of Forgac's method[1] for streptomycin assay, we developed a method of penicillin assay which is simple and ac-

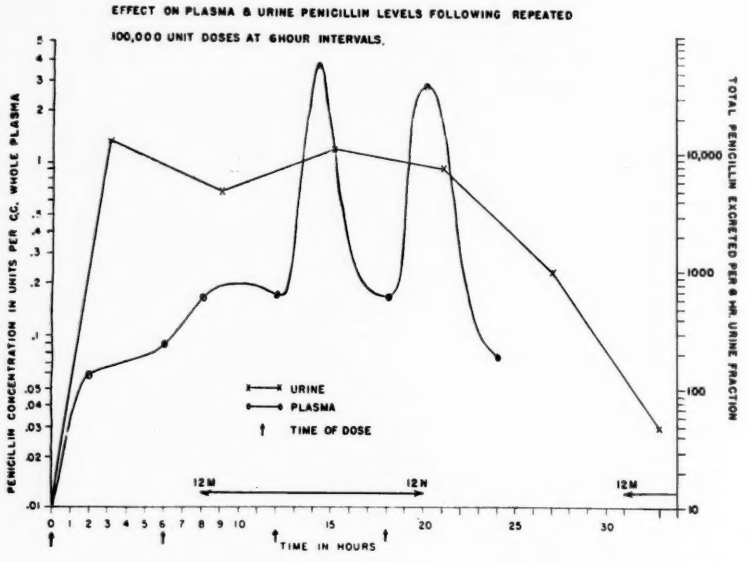


Fig. 6.

curate. With this method, fifty specimens may be prepared for analysis in two hours, and the penicillin concentrations read after four hours incubation at 39.5° C. Since this is a micro method, only ear lobe or finger tip blood specimens are necessary. The blood and urine penicillin concentrations following varying doses are shown in Figures 3-6.

Before using penicillin on patients, it was decided to add an antihistamine substance to the mixture, to decrease the chance of severe allergic pulmonary reactions. One per cent powdered Benadryl was used because it had a less disagreeable odor than other antihistamine substances. Analysis of 320 patients treated is shown in Table I.

### CLINICAL RESPONSE TO PENICILLIN TREATMENT OF INTRINSIC BRONCHIAL ASTHMA AND RELATED BRONCHIAL DISEASE

The fifty patients in this group responded in a similar manner to that described by many others who used inhalations of aerosol penicillin. We have been able to evaluate the temporary benefit only, since none of our cases have been followed longer than four months. We can say that penicillin-sensitive organisms are nearly always eliminated from the throat and sputum in a few days and in the majority of instances are replaced by coli-form organisms. Such organisms in the respiratory tract act as saprophytes. They persist for two to three weeks after treatment has been discontinued. *Practically* all bacteria may be removed from the respiratory tract temporarily by using mixtures of penicillin and streptomycin.

TABLE I. ANALYSIS OF PENICILLIN REACTIONS

1. Gross incidence of allergic reactions in 320 cases = 18 = 5.6%.
2. Gross incidence of local allergic reactions† in 320 cases = 15 = 4.7%.
3. Gross incidence of general allergic reactions* in 320 cases = 3 = 0.94%.
4. Incidence of previous allergic state among patients developing penicillin sensitivity. 18 cases sensitized, 11 cases with evidence of previous allergic state = 61%.
5. Gross incidence of local allergic reactions in 51 cases of chronic pulmonary disease = 11 = 21.5%.
6. Gross incidence of general allergic reactions in 51 cases of chronic pulmonary disease=1=2%.
7. Average time of appearance of local allergic reactions after start of treatment is 8 to 10 days. Earliest at 4 days, and latest at 14 days.

†Local allergic reaction consists of any one or combination of the following: Soreness, redness, swelling or occasional vesicle formation of the pharynx, tongue or larynx.
*General allergic reaction consists of urticaria, arthralgia, flare-up of pre-existing epidermophytosis, angioneurotic edema, pulmonary edema or asthma.

Clinically, the favorable response reported by patients is the reduction in cough and decrease in amount of sputum production and relief of asthma in many cases. Seven to fourteen days of penicillin or penicillin-streptomycin therapy produces a remission for a period of one to eight weeks in most cases. The daily dosage varied from 50,000 to 200,000 units per day, given in divided doses two to six times a day.

Micronized Benadryl used alone or mixed with vasoconstrictors, such as Neosynephrine or Propadrine, have been found to be effective symptomatically in asthma and should be useful in hay fever. Several patients have obtained relief in five to fifteen minutes; the relief lasted one to eight hours after one inhalation of 1/20 to 1/10 the usual oral dose. This relief is associated with an increase of vital capacity from 100 to 500 c.c.

We have just begun to explore the effect of inhaling various micronized antihistamines, vasoconstrictors, and powdered cough mixtures. The preliminary results have been better than anticipated.

## DISCUSSION

There have been no definite allergic pulmonary reactions to penicillin, such as asthma, pulmonary edema or anaphylactic reaction. We have seen approximately 5 per cent allergic sore throats, characterized by redness, swelling, and occasionally, vesicle formation, mainly in atopic individuals. This local allergic reaction usually appears after four to fourteen days of continuous treatment, and subsides in two to five days when penicillin is discontinued and moderate doses of antihistamine are given by mouth or applied locally. If penicillin is readministered to such patients after a period of two to eight weeks, the same reaction is likely to appear, but its onset is sooner than after the initial course of treatment. Even in these cases, no allergic pulmonary reactions were encountered. In a series subsequent to the 320 cases here reported, it has been found that by instructing patients to take a few swallows of water immediately following each treatment, the incidence of local allergic sore throat reaction is greatly reduced. We attribute this effect to the removal of the high concentration of penicillin from the throat. This removal of the penicillin reduces the possibility of its causing an irritation or allergic reaction.

We have seen the usual serum disease-like reactions to penicillin in slightly less than 1 per cent of the total cases, consisting of urticaria, arthralgia, and general malaise. In one case, it was possible to desensitize the patient by daily inhalations of small amounts of penicillin. Another allergic manifestation seen was the exacerbation of pre-existing fungus infection of the feet and hands. This reaction did not preclude the continued administration of penicillin when the local infection was treated simultaneously with a fungicidal ointment and antihistamine substance by mouth. In two patients, a moderately severe angioneurotic edema of the lips and face occurred, associated with a sore throat reaction. Both reactions subsided readily on antihistamine substance by mouth. Sore, red tongue appeared in some patients treated for more than ten days. The tongue had the appearance of vitamin B deficiency, and responded to treatment with liver and vitamin B complex intramuscularly.

## SUMMARY

1. Micronized potassium penicillin, mixed with 1 per cent Benadryl plus a vehicle of glucose or blood plasma, has been used in 320 cases.

2. A 4.7 per cent incidence of allergic sore throat reactions and 0.9 per cent rate of generalized sensitivity reaction has been observed.

3. There have been no definite pulmonary reactions of allergic nature.

4. This method of giving antibiotics is particularly efficacious in diseases of the respiratory tract and can be self-administered effectively and painlessly.

5. Micronized Benadryl drugs alone or in combination with vasoconstrictors give symptomatic relief in asthma.

6. This method is simple, economical, self-administered, eliminates injection, and is preferred to injection by the majority of patients.

ADDENDUM: Subsequent work has shown that the use of finger tip blood often shows false positive B. Subtilis inhibition, probably due to hemolysis and tissue juices. Further, Sodium Penicillin preparations, in comparable doses are much more rapidly absorbed and excreted.

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*Los Angeles 24, California*

# Southeastern Allergy Association

## *Meeting of January 18-19, 1947*

Papers presented at the second annual meeting of the Southeastern Allergy Association held in Atlanta, Georgia, January 18 and 19, 1947, are published here in abstract form as a record of the proceedings of the Association.

The paper entitled "Allergenic Problems of the Gastrointestinal Tract," by J. A. Rudolph, M.D., and Charles V. Sage, M.D., is published in full elsewhere in this issue.

### DIFFERENTIAL DIAGNOSIS OF ALLERGY AND INFECTION IN RELATION TO THE PARANASAL SINUSES

**RALPH V. ELLIS, M.D., F.A.C.A.**
**Greensboro, North Carolina**

THE frequency with which allergic inflammation of the paranasal sinuses is confused with infection in these areas is stressed. The large amount of needless surgery done without benefit upon allergic sinuses is deprecated. Criteria for the differential diagnosis of allergy and infection relative to the paranasal sinuses, including data obtained by inspection of the nasal cavities, cytological studies of nasal smears, roentgenograms and erythrocyte sedimentation rates, are reviewed.

These criteria were applied to 100 consecutive patients with nasal complaints seen in the Eye, Ear, Nose and Throat Clinic of the Students Health Service at the University of Minnesota. Thirty-one (31 per cent) of the series presented cloudiness of the antra by x-ray, yet in only eleven of these was infection demonstrable. The sedimentation rate was elevated in all for whom infection was proved. The sedimentation rate done by the Westergren method was arbitrarily adjudged slow when less than 5 mm. for one hour. Seventy (70 per cent) of the 100 cases by this standard had slow rates, and, of these, sixty-eight were demonstrably allergic. Sixteen patients had cloudiness of the antra and slow sedimentation rates. All of these proved to be allergic and without infection.

It is concluded that the erythrocytes sedimentation rate furnishes information of greatest value in differential diagnosis of allergy and infection of the paranasal sinuses.

### SIGNIFICANCE OF SKIN TESTS IN SUSPECTED DRUG SENSITIVITY

**O. C. HANSEN-PRUSS, M.D., F.A.C.A., and W. E. LEEPER, JR., M.D.**
**Durham, North Carolina**

THE failure of any single method of testing to prove applicable in all types of drug hypersensitivity has caused many physicians to abandon all forms of testing for sensitivity to simple chemicals. The cause for this pessimism, and its remedy, will be found in a careful analysis of the na-

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

ture of drug allergy. The distinguishing feature of this form of hypersensitivity is the character of the antigen. Being nonprotein, these simple substances must combine with protein to become antigenic. The second peculiarity is comparable to that attaining in food allergy. The drug is often administered by mouth and is subject to the processes of digestion, absorption, and metabolism. These processes may alter the nature of the antigen so that it (in its final active form) may differ greatly from the pure drug. This may account for the frequent failure of methods of testing which utilize the pure drug. The third distinguishing feature is the apparently very low titers of specific antibody present in the circulating blood. If these peculiarities of drug allergy are taken into consideration, more or less standard techniques can be selected for its demonstration.

The patch test is often positive in the cutaneous forms of drug allergy and, in particular, in arsenical sensitivity. It is specific in contact sensitivities. False positive reactions are caused by the primary toxicity of the compound.

The intradermal test is comparable to the patch test but of less value.

The application of the suspected substance to the tongue or buccal mucous membranes may result in local or systemic reactions of diagnostic significance.

The conjunctival test is especially valuable in determining diodrast sensitivity.

The leukopenic index following oral administration of drug may be of value but has not received a careful trial.

Readministration of the drug is the method of choice whenever the allergic disorder is not of such severity as to endanger life or threaten permanent damage. For demonstrating sensitivity to the coal tar derivatives, mixtures of the pure drug and human serum often produce a typical erythema and wheal when injected intradermally. Presumably these mixtures contain a drug-protein combination which acts as an antigen.

Leftwich's basic work on sulfonamide sensitivity has shown that the serum of individuals receiving these drugs in therapeutic amounts for five or more days contains an antigen which produces a positive intradermal reaction in individuals sensitive to these drugs.

The usual passive transfer test is of little or no value in drug allergy. The reverse technique of administering the antigen by mouth after preparing the skin with the serum of a sensitive individual will often detect very low antibody titers and may, therefore, be useful in the study of drug allergy.

It is believed that a careful analysis of each case will indicate which of these methods or which modifications of these methods will prove applicable to that case and that it will often be possible to identify the responsible drug.

## BRONCHIAL ASTHMA — DIFFERENTIAL DIAGNOSIS

### Report of Two Cases of Bullous Emphysema

MASON I. LOWANCE, M.D., F.A.C.A., EUGENIA C. JONES, M.D., WARREN B. MATTHEWS, M.D., and EDGAR M. DUNSTAN, M.D.
Atlanta, Georgia

FIVE cases are presented, illustrating typical diagnostic problems encountered in the study of bronchial asthma. Two cases present the picture of bullous emphysema. In one case, this was unilateral; in the other, it was bilateral and also accompanied by the presence of pulmonary tuberculosis. One case presented bronchial asthma with subsequent development of chest pain and a mass in the right chest.

Surgical interference demonstrated a mass of omentum herniated through the anterior epigastric foramen into the interlobar fissure between the right middle and lower lobes. One case presented a picture of bronchial asthma with a superimposed cardiac asthma, cardiac decompensation, and coronary occlusion. One presented the picture of carcinomatosis with onset of asthma a few years previously.

A review of six recent articles is presented.

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## X-RAY THERAPY AS AN ADJUNCT IN THE TREATMENT OF BRONCHIAL ASTHMA

### Preliminary Report

KATHERINE BAYLISS MACINNIS, M.D., F.A.C.A.
Columbia, South Carolina

A REVIEW of the literature reveals that x-ray therapy has been used for the relief of bronchial asthma for a number of years. Most of the patients treated have been classed as having severe attacks of asthma for long periods of time. Treatments have not been directed to just one area of the body, but have included the sinuses, chest, spleen, thyroid, pancreas, liver, adrenals and cervical sympathetics, with equally good results obtained. Relief has been noted in 40 to 75 per cent of cases treated.

We have run a small series of cases on children, giving them treatments every five days for four exposures. This was then followed by one exposure every month for four months. The results have been most remarkable in 75 per cent of the cases. X-ray films at the end of six months show considerable improvement over those taken just prior to beginning the treatments. These pathological findings as presented in the slides substantiate the clinical observations.

# THE ALLERGIC CHILD

**W. L. RUCKS, M.D., F.A.C.A. (Assoc.)**
**Memphis, Tennessee**

THE early diagnosis and institution of proper treatment of allergy in infants might prevent many serious emotional and physical handicaps in later life.

Every physician should recognize the allergic significance of colic, food and formula disagreement, regurgitation, repeated upper respiratory infections and dermatoses in infants, and, of no less importance, a family history of allergy.

Allergic symptoms may be so mild that the child can carry on without appreciable difficulty, or, following removal of tonsils and adenoids, the symptoms may be relieved for years, only to return subsequently. It is the chronic or untreated cases that lead to trouble in later years.

Some of the more common manifestations of allergy arise from functional imbalance of the autonomic nervous system, among them, allergic coryza, asthma, eczema, and diverse anaphylactic reactions. The location of the shock organs are considered responsible for the different types of reactions produced. Pharmacologic reactions which stimulate or depress the nervous system are of short duration. For the permanent relief of the patient, the causative allergen or allergens must be discovered and removed, or proper treatment must be instituted.

The effect of the autonomic nervous system on the acid-base balance is important, since children cannot withstand tendencies towards acidosis or alkalosis for an appreciable length of time. The early recognition of either of these symptom complexes and administration of necessary electrolytes to restore a proper balance may be life saving.

*Atopic Dermatitis (Eczema).*—Many cases of atopic dermatitis begin *in utero,* when the fetus becomes sensitized to foods eaten by the mother. Others are due to stock milk formulas. These children are allergic to a number of foods, to atmospheric changes, and a variety of contactants. The treatment is based upon correction of the diet, elimination of irritating contactants, prevention of infection and measures to make the patient comfortable. The mild forms respond to treatment readily, though the severe types tax the ingenuity of the physician.

*Sinusitis.*—The diagnosis of nasal allergy can be made from the history, the changes in the mucous membrane, roentgenograms of the sinuses, and the bacteriology and cytology of nasal and sinus secretions.

We have been particularly interested in the effect of infection and allergic reactions on sinus development. If ventilation and drainage are adequate, the sinuses develop normally. Further, sinus development follows a definite pattern at certain ages.

Sinus disease is often of allergic rather than infectious origin; in such cases, if conservative ventilation and drainage are accompanied by proper allergic treatment, development will proceed normally.

*Asthmatic Bronchitis.*—This condition presents a most difficult diagnostic problem. The history means more than the skin reactions. Every patient should have the most complete examination possible, and all infections which can initiate asthma should be ruled out.

The problem may be more difficult if the allergic condition is associated with some other type of chest disease. Case reviews illustrating some of these diagnostic problems are presented.

The treatment is an individual problem. It should include immunization against contagious and respiratory affections.

Educational programs for the medical profession, medical students and laity in the early recognition and treatment of the allergic child will give to this country fewer physically and emotionally handicapped adults. These programs are vitally important if allergy is to take its place in preventive medicine.

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## THE MEDICAL MANAGEMENT OF ATTACKS OF BRONCHIAL ASTHMA

**W. C. SPAIN, M.D.**
**New York, New York**

THE management of attacks of bronchial asthma is usually both immunologic and therapeutic. The immunologic measures include the identification, by history or by test, of the specific eliciting agents, and their removal or avoidance. Where such procedures are unsuccessful, immunizing hypodermic injections of the specific agents are given. However, this discussion is not concerned with these procedures but rather with the therapeutic measures found necessary.

Attacks of bronchial asthma may be (1) mild, (2) severe, (3) intractable. In the mild cases, usually reversible, with a fleeting edema of the bronchial mucosa as the chief pathologic feature, vasoconstrictor drugs are indicated, such as ephedrine and epinephrine, the former orally, the latter by injection or by nebulization. In the severe cases, such drugs also are indicated, but the secondary pathologic changes of hypertrophy of bronchial mucosa, with increased bronchial secretion, and often with bronchiectasis, require expectorant drugs, such as the iodides and ammonium chloride. Epinephrine in oil or in gelatin, to retard its rate of absorption, may be required. Oral, rectal or intravenous doses of aminophyllin are often helpful. Stramonium nitrite is often helpful. Codeine may be required for the excessive cough. X-ray therapy is useful in some cases, but heat

therapy seldom. Purgation, semi-starvation, and bed rest are valuable adjuncts.

In the intractable cases, in addition to these measures, oxygen by catheter or by mask or tent is required. Helium may be added. Ether in oil, rectally, may help. Glucose or glucose saline, intravenously, will combat dehydration. Demerol is useful. The antihistaminic drugs aid in a few cases. Sulfonamides and penicillin infrequently aid in bacterial cases by combating the infection.

Drugs to be used with caution, if at all, are atropine or belladonna, which dry the bronchial secretions; morphine, which suppresses the cough reflex or the respiratory center, and aspirin (with other coal tar drugs), to which occasional patients are violently allergic.

Drugs of little or no value in the treatment of bronchial asthma are calcium, potassium chloride, histamine and histaminase.

## PULMONARY TUBERCULOSIS AND ALLERGIC ASTHMA

**NORMAN VAN WEZEL, M.D., F.A.C.A.**
**Foley, Alabama**

THE author stresses the importance of adequately controlling the allergic asthma, in order that the tuberculosis may be controlled by collapse therapy.

The type of collapse therapy used will depend much on the absolute prevention of asthmatic attacks. These allergic states must be studied completely and treated by all means, symptomatically, eliminative, and by hyposensitization therapy.

Ten cases are presented which illustrate the difficulty in the diagnosis of asthma in the presence of tuberculosis, the forms of surgical therapy directed toward the control of the tuberculosis, and the dangers of such therapy during asthmatic attacks.

Although the incidence of the two conditions occurring in the same individual is low, the problem that these conditions produce taxes the ingenuity of the physician. The ten cases represent the experience covering the various problems encountered.

## THE IMPORTANCE OF PREDISPOSING AND CONTRIBUTORY FACTORS IN AN ALLERGIC EVALUATION

**NELSON ZIVITZ, M.D., F.A.C.A.**
**Miami Beach, Florida**

IN an allergic evaluation of a patient, skin testing is one part of the search for the exciting agent or allergen. The value of history and conversational study cannot be stressed too much in this evaluation. However, the search for an antigen is an incomplete approach for many patients, and

when this is the total extent of the study, there will be many failures. This is particularly true for foods and drugs but also with pollens and inhalants.

A group of fifty cases are considered, in which eighteen (36 per cent) could not be evaluated or treated properly without attention to predisposing and contributory factors. Furthermore, only the knowledge of these factors will explain the variable reactions to an antigen.

The importance of the home environment in a child, particularly where the parents are highly emotional or where asthma is prevalent, is stressed. The constitution of an individual in general and the skin in particular are exemplified by illustrations of patients. Glandular factors such as premenstrual tension are found to be definite auxiliary factors in the production of symptoms in an allergic individual. Also the relation of hormones on the neurovegetative functions of the body and allergic disease are mentioned.

The altered state of the gastrointestinal tract, by either disease or abnormal physiology from unwise eating habits, bears direct relationship to the allergic tolerance of the individual. One case with a mild pancreatic insufficiency and associated asthma from foods is discussed. It is suggested that reactions to food allergens may be due to variations in the physiology of the gastrointestinal tract, both normal and abnormal.

Both acute and chronic bacterial infections with their precipitating and complicating relationship to allergic manifestations are considered and illustrated by cases. It is pointed out that the same relationship exists with nonspecific irritation from vapors, smoke and odors.

Meteorological and climatic factors with specific reference to the fall of barometric pressure are discussed. It is mentioned that both treated and untreated patients are affected by such factors.

Finally, the psychosomatic factors are considered. It is suggested that psychic trauma be considered an allergen as are light and heat, which also fail to show an antigen-antibody reaction. But, regardless of the designation, psychic trauma is either a predisposing or a contributory factor in many allergic individuals, including those with specific proven sensitivities.

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## SOCIEDADE BRASILEIRA DE ALERGIA

We are pleased to announce that the Sociedade Brasileira de Alergia has been founded in Rio de Janeiro, Brazil.

The following officers were appointed for one year: President, Dr. U. Fabiano Alves; Vice President, Dr. Paulo Dias da Costa; First Secretary, Dr. J. Greves de Barros; Second Secretary, Dr. Eleuterio Brum Negreiros; Treasurer, Dr. Haroldo Cardoso de Castro; Librarian, Dr. Tamara Rubinstein.

The fiscal Board is composed of the following:

*Permanent Members*—Dr. Rafael Galeno Sidou, Dr. A. Oliveira Lima, and Dr. Olavo Gabriel Diniz.

*Substitute Members*—Dr. Percy Pereira dos Santos and Dr. Antonio Garcia Garbes.

# SPECIFICATIONS RECOMMENDED AS GUIDES IN THE COLLECTION AND PRESERVATION OF POLLENS

**Edited by MILTON V. VELDEE, M.D.†**
**Bethesda, Maryland**

## QUALIFICATIONS OF THE POLLEN COLLECTOR

The collector, or his immediate field supervisor, should have complete courses in college botany and plan taxonomy, or through practical training have acquired equivalent botanical knowledge.

## LABELING THE DISPENSING CONTAINER

The label on the final container should show the following:
The recognized botanical name for the plant involved.
The common name.
The amount of pollen in the dispensing container.
The year when the pollen was collected.
The name and address of the collector.

## PURITY OF THE POLLEN

*Freedom from Other Pollens.*—Contamination with mixed pollens of other species should not exceed 1.0 per cent, or 0.5 per cent with a single pollen, as determined by microscopic count, except that when ragweed pollen is the contaminant the amount of this pollen present shall not exceed 0.1 per cent. There are a few instances involving field-collected pollens when single species pollens cannot be collected to meet these specifications because simultaneously pollinating plants are growing in close proximity to each other. When unavoidable excessive contamination occurs due to this cause, the purchaser of the pollen should be informed.

*Freedom from Flower or Other Parts from the Same Species.*—The amount of extraneous plant material from the same species present in the pollen should not exceed 10 per cent for pollens obtained from those species which do not freely shed their pollens and not more than 5 per cent from free-shedding species.

*Freedom from Non-related Contaminants.*—Pollen should be free of all contaminants not related to the species of plant involved, such as leaves, dirt, and similar substances. An exception is recognized with those plants whose growing habits make contamination with dirt unavoidable; example, creeping pigweed.

## STABILITY OF THE ACTIVE COMPONENT OF THE POLLEN

Freeing the pollen of any extrinsic moisture (due to weather conditions such as humidity, dew, or rain) should commence just as soon as possible after collection. A delay of more than twenty-four hours should not occur when pollens are collected in the field. When plant material is brought to the pollen-collecting shed to await the shedding of the pollen, it is interpreted that evaporation of extrinsic moisture takes care of itself but can be accelerated by proper ventilation and heating of the collecting room.

†Chief, Biologics Control Laboratory, National Institute of Health, Bethesda 14, Maryland.
Co-operating in the preparation of these specifications are the following individuals and groups:
*Representing the allergists:* Committee of Therapy, The American Academy of Allergy; Subcommittee on Certification of Allergenic Extracts, American College of Allergists; and Doctors R. A. Cooke and R. F. E. Stier.
*Representing the pollen collectors:* Wm. B. Hafford, Fred H. Hodgson, Guy Hollister, Cleveland Sharp, and T. R. Stemen.
*Representing research:* A. Stull, R. P. Wodehouse, and J. J. Wright.

Drying the pollen to free it of intrinsic moisture (moisture naturally occurring in the pollen grain), while not as urgent as removing external moisture (see preceding paragraph), should nevertheless commence with a minimum of delay. With present methods of collecting and drying, this usually can be started within twenty-four hours of collecting the pollen in the field or after completion of shedding in the pollen-harvesting shed. It should never be delayed more than seven days with either method of collection.

Freshly field-collected pollen from which extrinsic moisture has not been removed should neither be packed in a compact layer nor in a closed container. Similarly, freshly collected plant material from which pollen is to be separated upon arrival at the pollen-harvesting shed should neither be packed in compact layers nor in closed containers, if the time required for transportation to the harvesting shed is more than one, two, or three hours, the latter depending on the species of plant. A successful procedure is to place the plant material in thin layers in trays made of wire screening which are then stacked so as to allow the free circulation of air between the layers.

Once drying has been started to remove intrinsic moisture, it should proceed without interruption at not over 65° C. (117° F.) until the moisture content is less than 1.0 per cent; for practical purposes this means until no further loss of weight occurs.

The age of a pollen is indicated by placing the year of collection on the label.

### TYPE OF CONTAINER

For bulk storage each pollen should be placed immediately after removal from the drier in a clear glass container fitted with a closure capable of excluding atmospheric moisture. Containers of equal quality should be used for the final packaging.

### CHANGE OF COLOR IN THE DRIED POLLEN

Properly dried pollen when contained in an adequately sealed container does not undergo further color change. An exception exists with some of the Compositae, as for example goldenrod, where there is a progressive color change for one or two months after drying before a permanence of color is reached.

### CO-OPERATION BETWEEN THE USER AND COLLECTOR OF POLLENS

The user of pollen for the preparation of allergenic extracts should estimate his needs so as to place orders with the collector in advance of the pollen season. This practice will make more certain the receipts of fresh pollen of good quality and in adequate supply. It is suggested that the user require the collector to certify that the stock supplied on order meets the specifications detailed above. A copy of these specifications might be enclosed with the order, with space provided for the collector's certification, and returned with the material. Another method would be for the manufacturing allergist to purchase pollens subject to meeting these specifications on receipt.

### COMMENTS ON THE SPECIFICATIONS

*Qualifications of the Pollen Collector.*—The collection of pollen, both as it relates to purity and the identification of each collection as to its correct botanical name, demands a certain training in botany. This is best obtained through proper academic training but could conceivably be obtained through practical experience in the field when acquired under competent supervision.

LABELING THE DISPENSING CONTAINER

The Linnean system of binominal nomenclature should be used in recording the botanical name.

When there is more than one common name, the one best understood by the allergist should be selected.

The amount of pollen in the container is preferably expressed in the metric system.

The age of the pollen should be made known to the allergist. This will continue to be important until the factors which cause loss of antigenic activity are known and can be eliminated.

The collector as used in this section means the primary distributor and does not refer to the particular individual who may have collected the pollen in the field.

*Purity of the Pollen.*—The contamination of a pollen with pollens of other species is objectionable because of the harmful effect it can have on the patient. If the amount of foreign pollen is sufficient, there is a real danger that the resulting extract will cause false reactions and lead to improper treatment of the patient. Pollens vary in their antigenic activity; ragweed being particularly active.

The contamination of a pollen with extraneous plant material from the same species will not lead to deleterious reactions in the patient. However, its presence will reduce the antigenic strength of a finished allergenic extract and therefore is objectionable.

The presence of dirt and other non-pollen substances is a good index of the collector's ability and professional standards. However, there are certain exceptions which must be recognized. The growth habits of some plants and the growing environment in certain instances make it very difficult, if not impossible, to collect the pollen without the admixture of dirt or soil. If this is made known to the producing allergist, corrections can be made at the time of preparing the extract.

*Stability of the Active Component of the Pollen.*—The factors which determine the stability of the allergenic component of a pollen are not fully established. However, it has been shown that storage without adequate drying speeds the rate of denaturation, and more particularly so, if stored at relatively warm temperatures. Extrinsic moisture (due to humidity, dew, or rain) provides favorable conditions for fermentation and souring of the pollen due to the activity of contaminating micro-organisms. Intrinsic moisture (moisture contained in the pollen) is necessary for enzymatic (chemical) activity within the pollen grain. These denaturing activities can be slowed, if not actually arrested, by storage at temperatures well below freezing or by the removal of the moisture to below the critical level for enzyme and micro-organism activity. Storage in an oxygen-free atmosphere would be of benefit. The age of the pollen is prabably of secondary significance, provided the moisture is promptly and adequately removed.

At the time of collection the pollen grains are living cells inside of which a certain amount of metabolic (enzymatic) activity is in progress. Intrinsic moisture is involved in this activity and may even be produced by being split off from other compounds during cellular metabolism. This intercellular activity has been termed respiration. The purpose of prompt drying (desiccation) is to arrest permanently this chemical activity.

An ideally treated and packaged pollen would be one which has been dried to less than 1.0 per cent moisture immediately after collection, followed by filling into final glass containers and then hermetically (flame) sealed under vacuo and stored at –20° C. These are requirements which cannot be obtained easily since pollens are field-grown and therefore must be collected where found. There is always the cost of production to be considered as well. However, having in mind the essentials for an

active pollen extract, it becomes possible to lay down collection and preservation procedures of a practicable character and which should add greatly to insuring the quality of the pollen.

The construction specifications of a very satisfactory drier, and its mode of operation, have been described by Benesford, and Cooke.† A drier of this design, or one of similar design and operating principle, can be constructed at relatively low cost and by a person with ordinary mechanical skill. A drier constructed on this principle must be thermostatically controlled, and preferably time-controlled. With these safeguards, drying may be accomplished without risk of damaging the allergenic activity. The drier is portable and therefore can be carried as field equipment on extended collection trips.

Another method is to dry the pollen in a glass vacuum desiccator of the usual laboratory type. This calls for phosphorous pentoxide ($P_2O_5$) as the desiccant and a source of vacuum, usually a water vacuum pump. When this method is used the operation is carried out at prevailing room temperature. The time interval, beyond the minimum required to bring the moisture content below 1.0 per cent, is not a factor, since no heat is applied. It is important that there should still be active phosphorous pentoxide exposed in the vacuum jar at the end of the drying interval.

Experience will show the observant collector how long it takes to reduce the moisture content to less than 1.0 per cent. As a practical objective this should mean until there is no further loss of weight. In addition, any collector desiring to have his drying method independently checked may do so by submitting no less than a 1 Gm. sample of dried pollen in one of his final dispensing containers to the Biologics Control Laboratory, National Institute of Health, Bethesda 14, Maryland. The large users of pollens, who usually have facilities for making moisture determinations, probably also would be glad to report the moisture content of at least some of their pollen purchases if a report were requested by the collector.

*Type of Container.*—In certain sections of the country the humidity is excessively high. Under such circumstances some collectors and users of pollen have found it advisable to provide their bulk storage containers with a desiccant. It may be placed in a specially constructed lid, or contained in a suitable cloth bag and hung immediately under the lid. Still another method is to store the bulk pollen containers in a compartment provided with a well-fitted weatherstripped door. Space within the compartment is provided for an open tray which is kept filled with a drying agent in active condition.

*Change of Color in the Dried Pollen.*—When pollens are properly dried, the color becomes fixed. Progressive color change after drying is completed is an indication of chemical change within pollen grains. This is likely to mean denaturation of the active principle. It should serve as a warning to the collector that his preserving methods are inadequate.

*Co-operation between the User and Collector of Pollens.*—It is becoming increasingly evident that many factors are at play in determining the allergenic activity of a pollen used in an allergenic extract. The allergist should profit by the well-controlled experiences which the pharmacologist has had with digitalis leaves. In this instance, it has been well established that the geographic area, the character of the soil, the amount of moisture during the growing season, the variety of the plant, the time of harvesting the leaves, and the method employed in their curing largely determine the therapeutic activity of the finished preparation. Without question,

†Benesford, Arthur B., and Cooke, Robert A.: J. Allergy, 15:379-384, 1944.

these same factors are at play with the pollens. The probability of controlling the growing conditions for each pollen is remote. It seems nearly as remote that methods for the accurate biologic assay of a pollen extract can be developed in the immediate future, though the study by Wodehouse† indicates some progress. However, much can be accomplished by a close co-operation and better understanding between the manufacturing allergist and the pollen collector. The acceptance of the above specifications of quality for the pollens will greatly improve the therapeutic activity of the finished extract. The collector should welcome these specifications as a code of operation for the pollen-collecting industry. As a corollary, the manufacturing allergist should be willing to accept the probable small increase in cost involved in collecting and preserving pollens in this way.

†Wodehouse, R. P.: Ann. Allergy, 5:203, 1947.

## ALLERGENIC (SKIN-TEST) ACTIVITY OF LOW RAGWEED POLLEN AFTER IRRADIATION OF EXTRACT WITH ULTRAVIOLET LIGHT

*(Continued from Page 10)*

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### ANNOUNCING A NEW BOOK

"Psychodynamics and the Allergic Patient" is the title of a new book, the first of a series of three, presenting the Panel Discussions given at the annual meeting of the American College of Allergists, to be published in July, 1948.

The historical chapter entitled "Psychosomatic Aspects of Hay Fever Prior to 1900," by Harold A. Abramson, M.D., will appear in the March-April issue of the ANNALS OF ALLERGY. Another chapter by Dr. Abramson on "Psychodynamics and the Allergic Patient" will appear in the May-June issue.

Contributors include Harold A. Abramson, M.D., Frank Fremont-Smith, M.D., Franz Alexander, M.D., O. Spurgen English, M.D., Sandor Rado, M.D., Edward Weiss, M.D., J. A. P. Millet, M.D., Rudolf L. Baer, M.D., Ethan Allan Brown, M.D., Hal M. Davison, M.D., M. Murray Peshkin, M.D., and Homer E. Prince, M.D.

This book will contain about 120 pages, with eight pages devoted to illustrations. Further announcement, including price and other details, will appear in the next issue.

# Editorial

*The opinions expressed by the writers of editorials in the* ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

## PRESENT STATUS OF CERTIFICATION

According to the resolutions passed at the business meeting of the Fourth Annual Meeting of the American Academy of Allergy in St. Louis, December 15, 1947, and previous action taken by the Board of Regents of the American College of Allergists, a committee appeared before the Advisory Board of Medical Specialties of the American Medical Association on February 7, 1948, in Chicago and presented the following resolutions:

To The Advisory Board of Medical Specialties

Gentlemen:

We, the signers of this petition, representing officially both the American Academy of Allergy and the American College of Allergists and therefore over 1,200 of the physicians of America who at this time are doing clinical allergy, met in Chicago on February 6, 1948, and passed unanimously the following resolution:

WHEREAS, the specialty of allergy since the turn of the century has kept pace with the growth and development of the basic sciences underlying medicine. With the increasing knowledge of immunology and tissue chemistry, the science of allergy now approaches its fiftieth year of development. And

WHEREAS, the clinical specialty of allergy now embraces 1,200 and more physicians who have and are now devoting most of their energies and most of their time to this specialty. And

WHEREAS, the incidents of allergic manifestations among the population at large affects at least 10 per cent of our people. And

WHEREAS, residencies and postgraduate instructional courses in allergy are multiplying yearly throughout the country and are training hundreds of physicians in this specialty. And

WHEREAS, the number of publications in the specialty of allergy is ever increasing. And

WHEREAS, the protection of both the lay and medical public is a responsibility which must be assumed by the allergists.

BE IT RESOLVED, therefore that we, who comprise this Joint Committee representing both the American College of Allergists and the American Academy of Allergy, unanimously agree to support the petition respectfully submitted to your Board by the American Academy of Allergy and the American College of Allergists to establish the American Board of Allergy.

Representing the
*American Academy of Allergy*

GEORGE PINESS, M.D.

HARVEY BLACK, M.D.

HARRY L. HUBER, M.D.

Representing the
*American College of Allergists*

HAL M. DAVISON, M.D.

FRED WITTICH, M.D.

M. MURRAY PESHKIN, M.D.

JONATHAN FORMAN, M.D.

## ANTIHISTAMINIC AGENTS IN ALLERGY

For the second time in a year, the New York Academy of Sciences held a conference of considerable interest for allergists on October 3 and 4, 1947, the subject being "Antihistaminic Agents in Allergy." The pharmacology of histamine and that of the antihistaminic agents was considered by an international array of speakers headed by Sir Henry Dale. The printed record, when presented, will offer a comprehensive review of our knowledge in these fields.

One aspect of the problems raised by the study of the effect of the new group of drugs (which came to us from France and which are now undergoing such a comprehensive investigation) merits some comment in this place. Though the pharmacological effects of the antihistaminic drugs are by no means restricted to antihistaminic action, this later one is evidently predominant in the present explanation of the clinical effect. Dr. R. L. Mayer attempted a quite original approach to the question, why these drugs should not be effective in allergic dermatoses of the type of contact dermatitis. Suspecting that in this case additional mechanisms may come into play, he found that hyalinuridase greatly enhances the reaction of dermally sensitized guinea pigs on dermal challenge. He then found that pyribenzamine and its congeners block this effect. These experiments, of course, do not prove that hyalinuridase plays a role in human allergic dermatoses. On the contrary one may argue that the lack of clinical effect of antihistaminic drugs speaks against such an effect. But whatever their significance for the action of the antihistaminic drugs, Mayer's data give a stimulating example of experimental analysis. And they will get the dermatologist to work on a hitherto unsuspected aspect of dermal pathology.

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## EFFECT OF RUTIN ON ANAPHYLACTIC AND HISTAMINE SHOCK

According to a recent article, rutin protects against anaphylactic shock. Raiman, Later and Necheles,† working at the Michael Reese hospital in Chicago, report that guinea pigs receiving 2 mgs. of rutin intraperitoneally thirty to forty-five minutes before anaphylactic shock was attempted, not only received protection against anaphylactic shock but also manifested no symptoms. These experiments were performed on three series of animals under different conditions. Of twenty-one guinea pigs, nine animals were given 1 mg. of rutin intravenously thirty to forty minutes before receiving the minimal lethal dose of histamine. All of the animals in this series died, exhibiting the characteristic symptoms of histamine shock. These results demonstrate that rutin protects guinea pigs against the fatal effects of anaphylactic shock but not against those of histamine shock.

†Effect of rutin on anaphylactic and histamine shock. R. J. Raiman, E. R. Later, and H. Necheles. Science, October 17, 1947.

The authors point out that if it is assumed that rutin protects against anaphylactic shock by virtue of its "tightening effect" on the capillary endothelium, then histamine may be excluded as the lethal factor of anaphylactic shock. In the guinea pigs injected thirty to forty minutes before anaphylactic shock was attempted, no bronchiolar spasm was apparent. Their lungs were found to be normal. On the other hand, histamine injected produced the syndrome of protein anaphylactic shock with bronchiolar spasm and changes in the lungs. According to the authors, the possibility exists, that the protective effect of rutin may be that it prevents the liberation of endogenous histamine by unknown factors other than those which increase capillary permeability. It may be recalled that Hiramatsu found that guinea pigs were protected against anaphylactic shock by large doses of hesperidin.

Irrespective of the way in which rutin acts, it is apparent that the simple histamine theory of allergy requires extensive modification since, with increasing knowledge, its foundation becomes increasingly less certain.

## PHYSIOLOGY OF THE LUNGS AND THE ASTHMATIC STATE

Although allergists have been primarily interested in immunological mechanisms and more recently in those connected with psychodynamics, it should not be forgotten that the physiology of the lungs is of prime importance in elucidating the many phenomena connected with the asthmatic state.

A recent paper by Mack, Grossman and Katz (Am. J. Physiology, 150:654, 1947) points out how pulmonary congestion may operate to bring about dyspnea. Mechanically, one of the important factors is the change in the distensibility of the lung. When the pulmonary vessels become engorged, their rigidity increases. Thus, they act like a hose turgid with water under pressure. It is readily accepted that this may be a contributing factor in the increased respiratory effort observed in congestive heart failure. But this diminished distensibility also may contribute to a diminution in vital capacity and even to the formation of intrapleural transudates.

Mack, Grossman and Katz demonstrated directly the effect of congestion of the pulmonary vessels on lung distensibility with fresh lung preparations obtained from dogs and in the intact animal. They found that the injection of blood into the pulmonary circulation causes a decrease in the distensibility of the lung proportional to the amount of blood introduced. When almost all of the blood injected was siphoned off, the distensibility curve was restored. This demonstrated clearly that the effect was due to intravascular blood which could be siphoned off, and not to an intra-alveolar transudate similar to that found in pulmonary edema.

*(Continued on Page 93)*

# Progress in Allergy

## BRONCHIAL ASTHMA (IV)
### Critical Review of Literature

LEON UNGER, M.D., F.A.C.A., and BENJAMIN F. GORDON, M.D., F.A.C.A. (Assoc)
Chicago, Illinois

In the eighteen-month period from January 1, 1946, to June 30, 1947, there have been published new books and a large number of articles which deal with various kinds of asthma and its closely related clinical conditions. These will now be reviewed in much the same way as in the previous reviews on this subject which covered the literature of 1943,[349] 1944,[350] and 1945.[351]

Some of this literature is not new, but much is devoted to the increased use of penicillin and the so-called antihistaminic drugs. The authors have faithfully tried to cover all the articles on the subject from all over the world. We realize that we have omitted some and beg the authors' indulgence. Some journals cannot be obtained, but most of the omitted articles are written in languages foreign to us and we have not been able to obtain satisfactory translations. We therefore suggest to authors who write in Spanish, French, German, Russian, Portuguese, Scandinavian, et cetera, that they end their articles with a comprehensive summary in English. This will insure proper credit in the future. Incidentally, those who write in English might reciprocate. We would also be pleased to receive reprints, with translations or abstracts, of foreign articles.

#### NEW BOOKS

Arranged in alphabetical order, twelve new books have been written either on asthma or on various phases of allergy, including asthma.

Gianfranco Capuani[56] has written an 829-page book on *Allergia e Malattie Allergische.* The book was published in Torino, Italy. It is an excellent volume, with a good discussion of fundamental and clinical subjects, well-illustrated, and with an extensive bibliography.

Cooke's volume[74] on *Allergy in Theory and Practice* has attracted much favorable comment and some opposition. Dr. Cooke wrote most of the book, but thirteen associates contributed some chapters. The fundamental and theoretical aspects of allergy are excellently portrayed, though some readers do not believe that the role of infection is as important as stated. Skin testing is practically only by the intradermal method, a serious error because of possible constitutional reactions. The chapters on bronchial asthma are good but not adequate as regards details of treatment.

*It's An Allergy,* by Crandall,[75] is a comprehensive book on allergy written for the patient, with a chapter on asthma. It gives good advice to the patient, and its large bibliography may lead some patients to learn more about their allergies. This may or may not be a blessing, depending on the patient. There are interesting case reports.

*The Treatment of Bronchial Asthma,* by Derbes, Engelhardt, and their associates,[88] is a good book. The first eight chapters are devoted to basic material, including good chapters on anatomy, physiology and pathology of the respiratory tract. In the next fifteen chapters there is a discussion of intrinsic and extrinsic factors in bronchial asthma. Worthy of special mention are the chapters on the role of foods by Wittich, differential diagnosis by Sodeman, nonallergic treatment by La Due, and statistical survey by Dublin and Marks. Because of its size, some details of treatment are necessarily omitted. A larger revision by these authors, with a more extensive bibliography, would be welcome.

Feinberg's *Allergy in Practice,* second edition,[109] contains much new information, especially as regards mold allergy, vascular allergy, and tropical eosinophilia. There is an informative chapter on histamine by Dr. Carl Dragstedt, and an extensive and excellent chapter on pollens by Durham. Some of the newer information on asthma is also listed, as well as information on histamine antagonists.

*Alergia en la Practica Clinica,* by Fuentes, Recarte, and Graña,[131] from Montevideo, Uruguay, is a large and pretentious book on all aspects of allergy. In addi-

Review covers period from January 1, 1946, to June 30, 1947.

tion, there are chapters on hydatid diseases, eosinophilia, and lymphogranuloma inguinale, and much on tuberculin allergy. The book is well written and should be translated into English and other languages. Like most contributions from South America, it emphasizes the predominant role of foods. Inhalant allergy seems much less important than in North America.

Leslie Gay's *Diagnosis and Treatment of Bronchial Asthma*[148] gives the experiences in this field of one of the pioneers in the field of allergy. There are excellent discussions of the physiology, pathology and psychosomatic aspects of asthma, with case reports. The book is rather small, and because of excessive space given to particular subjects, the author has been forced to curtail discussion of many more important points relative to bronchial asthma. The reader is urged to consult the book reviews.[137]

*Diseases of the Chest With Emphasis on X-Ray Diagnosis*,[295] by Rubin and Rubin, is an outstanding work. The illustrations, with twenty-four plates in color, are excellent. Both pulmonary tuberculosis and nontuberculous diseases of the chest, including asthma, are discussed. There are excellent chapters on surgical treatment of empyema, lung abscess, cancer, tuberculosis, and benign tumors. Two chapters are devoted to obstruction of the bronchi.

*What You Don't Know May Hurt You*[297] is a small volume by Rudolph and Rose. By case reports and simple, humorous language the laity is informed about some phases of allergy. Some reports are rather sensational, but this aspect is probably necessary to interest the public.

*Asma Alergia* (Asthma Allergy), by Ruiz-Moreno,[298] contains 186 pages; the first 139 are given to asthma, the rest to allergy in general. The book is small but contains much information, some old, some new. Chapter X is interesting because it deals with social problems of asthma, including eugenesis, legislation, asthma in military service, prophylaxis (industrial), and professional re-education.

Sterling has written another small book entitled *Clinical Allergy*.[327] Case reports are interesting but important details are lacking.

Last, but by no means least, is that tremendous book entitled *Allergy*, second edition, by Urbach and Gottlieb.[352] This edition is even better than the first. There are over 3,300 references, a thousand more than in the previous edition. The book is extremely valuable because it covers the entire field of allergy. A great deal of new material has been added, including sections on psychosomatic aspects and drug allergy. A large part of the book is devoted to dermatologic conditions. The only part of the book open to American criticism is the continued thinking and terminology of the European; these things never have and probably never will be accepted by those of us trained in the United States.

These reviewers earnestly advise future authors of books to write very large books if they wish to cover the entire field of allergy. If an author concentrates on a limited subject, such as bronchial asthma, hay fever or migraine, his work should still be large enough so that the reader can obtain sufficient information to help him in his particular cases. A good bibliography is absolutely essential, and it should be broad minded so that both sides of the question can be represented.

### MILITARY REPORTS

The number of articles from the armed services is naturally decreasing. The war is over, but inasmuch as some of our forces are still scattered over the world, we must continue our interest in the military aspects of asthma and other allergic diseases. Asthma is the main allergic cause of disability and discharge.

A wonderfully satisfactory report concerns the incidence of tetanus in the United States Army in World War II. Long and Sartwell[223] report that tetanus toxoid was given to all except a few who were very sensitive to it. After immunity was established, booster or stimulating doses were given at the end of one year and for injuries. Adequate response to booster doses was observed for a period of at least three years after basic immunization and for two years after the routine stimulating dose. The protection probably lasts even longer.

Throughout the entire war period there were only twelve cases of tetanus in the entire army, including four from injuries sustained prior to entry into active duty. Only six of these had received basic immunization, and only four had the emergency stimulating dose. Death occurred in five of these twelve patients; of these, two had received full prophylactic immunization plus emergency booster doses after injury.

Compared with the incidence of tetanus in World War I and in the intervening years with (1) civilian mortality, (2) incidence in enemy forces, and (3) incidence in civilians injured during military operations, it is gratifying to note that the army's preventive treatment was highly effective. Reactions from tetanus toxoid were

infrequent, and when certain peptone components were removed, reactions dropped to a frequency of less than 2 per 100,000 injections.

Two reports come from the U. S. Navy. Blue,[35] in an article on allergy in the Pacific, concludes: (1) There is an apparent increase in allergic conditions in the armed forces. (2) Psychogenic factors are of greater importance than in civilian life (this point is emphasized in almost all reports from the services). (3) The allergic conditions themselves are about the same in the Pacific area and in Continental U.S.A. (4) Of 500 patients, 293 (58.6 per cent) had bronchial asthma, and fifty-six (11.2 per cent) had hay fever. (5) The average duration was eight years. (6) As regards asthma, 17.4 per cent had their first symptoms in this area, and in 86.6 per cent symptoms were aggravated while in the Pacific. (7) In 61.3 per cent of the asthmatics, good results were obtained, but, because of military necessities, only 15.7 per cent were returned to duty; the rest were sent home as unfit for combat duty.

Smith[318] concludes that bronchial asthma cannot be successfully treated in a military environment where many factors are beyond the control of the physician. In a study of 100 cases of chronic asthma, he found that it caused disability over longer periods of time than most illnesses (average time on sick list was 114.5 days per patient). Seventy-eight per cent of these asthmatics had a positive pre-enlistment history of asthma. Skin tests were positive in 70 per cent, and 41 per cent cleared under treatment, yet as with Blue, only 18 per cent were returned to duty. These figures bear out the wisdom of the navy in not knowingly accepting men with pre-existing asthma.

There are five reports from the army, and the similarity in these and in those analyzed in previous years[349-351] is striking. Fishman[115] studied 100 asthmatics returned from the European Theater of Operations (North Africa, Italy and France). All were evacuated because their asthma prevented them from performing even limited duties in the service. Fishman divided them into three groups:

(A)—(Fifty-six cases) No history of previous asthma before overseas arrival.
(B)—(Fourteen cases) An initial attack in civilian life followed by an asymptomatic period which was terminated by arrival overseas.
(C)—(Thirty cases) Recurrent asthma in civilian life which became incapacitating overseas.

No symptoms were present in seventy-eight when they reached the United States, and these needed no further treatment. Emotional factors were especially severe in eighteen cases and were much more important in Group A. Groups B and C were composed of individuals who fully satisfy the diagnostic criteria for allergic disease (high percentage positive skin tests, previous attacks of asthma, higher percentage positive family history). Asthmatics constituted 1 to 3 per cent of the total number evacuated to the United States—this despite all efforts to keep asthmatics out of the army.

Winkenwerder[373] agrees that 1 to 2 per cent of admissions to his hospital in the Southwest Pacific Area were for asthma. He studied 209 cases, most of whom gave a positive personal or family history for allergy and/or gave positive skin tests. Of 102 patients whose attacks began in the service, in 64 per cent, the first episode occurred in the tropics, in 16 per cent in Australia, and in 20 per cent in the United States. In the tropics, hay fever was associated with the asthma in about 50 per cent of cases. Symptoms were usually perennial, and many developed asthma within two weeks after arrival in the tropics, the majority within three months.

The chief allergens: grass and algeroba tree pollens, mold spores, and tropical dust, which has about twenty times the protein nitrogen content as compared with dust in the United States. Contributory factors included excessive humidity, wide variations in daily temperature, strong aroma of molds, and the vigors of military life. The average disability period per man was about two months, and 82 per cent had to be returned to the states.

Rosen[294] studied 100 asthmatics admitted to an army hospital from June, 1944, to March, 1945, with an average stay of one month. Mild symptoms occurred in nineteen, moderate in seventy-four, severe in seven. The first group was put on limited duty; the rest were discharged from the service.

One patient had a coincident asthmatic bronchitis; all the rest had uncomplicated bronchial asthma. There were no deaths. Asthma was perennial in eighty-seven, seasonal in thirteen. Associated nasal symptoms were present in fifty-five cases, thirty of which were perennial and twenty-five seasonal. One interesting point was

that the first attack of asthma in seven of ten ragweed asthmatics occurred at the camp; these seven came from areas with less previous exposure to ragweed to this hospital which was located in a part of Indiana noted for the highest ragweed pollen counts.

In another article, Rosen[293] compared asthma in fifty patients returned from the tropics with fifty who had not been outside of the United States. In the first group, 40 per cent had their first attack of asthma while in the tropics; in the U. S. group, only 14 per cent had their first attack after induction. There was no great difference in blood eosinophilia (5 per cent or over) between the two groups (42 per cent and 32 per cent), and x-rays of the chest were normal in 84 and 82 per cent, respectively. On skin testing, 42 per cent of the "tropical" group reacted to timothy, with only 26 per cent in the U. S. group; on the other hand, reactions to feathers were six per cent and 24 per cent, and the U. S. group also showed more positive reactions to food extracts.

Zoss[380] and his associates studied the nasal, sinus and bronchoscopic findings in 250 soldiers who had perennial asthma and were stationed in Georgia. Of these, 81.4 per cent had been overseas. More developed asthma for the first time while in the Southwest Pacific than in either the European or China-Burma-India sectors. Of the entire group, 43.2 per cent had asthma for less than five years.

Examination revealed that 50 per cent of the patients had chronic suppurative sinusitis. Bronchoscopic examinations were done in all cases and revealed abnormalities in 89.6 per cent. The authors divided these: (1) chronic suppurative bronchitis in 49.2 per cent, (2) chronic nonsuppurative bronchitis in 38.8 per cent, and (3) allergic bronchitis in 1.6 per cent. In the whole group, chronic respiratory tract infection was found in 73.2 per cent.

[These high percentages as regards infection are extremely surprising. It is hardly likely that military service can be of that much importance in this regard. The authors admit that cytological and bacterial investigations of the bronchial secretions were not done in all cases, due to circumstances beyond their control. Are we to rely on observation of the nasal and bronchial mucosa alone to say whether infection or allergy or neither exists? The authors state that "the finding of mucopus was considered reliable evidence of bacterial infections." This is not true, as shown by Hansel and others, who have pointed out over and over again that a predominence of polymorphonuclear cells in the nasal secretion indicates infection, whereas eosinophilia occurs in allergic rhinitis. Similar findings occur in sputa. If infection had really been so frequent in these young asthmatics, they should have had elevation of temperature, leukocytosis, and an increased sedimentation rate, and they should have been helped by chemotherapy (authors report little benefit).]

### TROPICAL EOSINOPHILIA, LOEFFLER'S SYNDROME, PERIARTERITIS NODOSA

Confusion still exists in differentiating these three conditions. High blood eosinophilia remains outstanding. Are they related? The reader is urged to study again the discussions in the three previous reviews.[349-351]

*Tropical eosinophilia* continues to be interesting. As stated previously,[351] it "occurs chiefly, but not exclusively, in the tropics, especially in India. The chief symptoms are an insidious onset, with malaise, low-grade fever, headache, and unproductive cough; wheezing and dyspnea are often associated. Leukocytosis (up to 60,000) and marked blood eosinophilia (up to 89 per cent) are striking features. Chest x-ray films usually show fine mottling in both lungs. One to six intravenous injections of neoarsphenamine or other arsenical product cause prompt relief with disappearance of leukocytosis, eosinophilia, and the so-called 'asthma.' No causative organisms have been found."

New reports emhasize that the disease is not confined to India. Wilson[371] did differential white counts in a consecutive series of thirty-four patients attending the native civil hospital in Dar-es-Salaam, Tanganyika, East Africa. These persons had symptoms of recurring bronchitis or asthma. In six, the eosinophilia ranged from 40 to 78 per cent. This group and a seventh patient who had an unexplained eosinophilia had tropical eosinophilia. Six were treated successfully with arsenic; the seventh recovered spontaneously. The characteristic picture consisted of cough, wheezing, and low-grade fever, separated by periods characterized by morning spasmodic cough. Wilson does not believe this condition is the same as Loeffler's syndrome.

Blue[35] noted that four of his patients in the Southwest Pacific had tropical eosinophilia. In all cases, epinephrine relieved attacks of "asthma," but complete relief and reduction in blood eosinophilia followed arsenical therapy. One patient had been in

Shanghai, and all had been in New Zealand, Samoa, and the Wallis Islands. Despite extensive search, no parasites were found.

Irwin[179] reviews previous findings and adds two new cases in soldiers who had returned after duty in the Southwest Pacific. Their symptoms and laboratory findings were similar to those reported by others, and careful clinical and laboratory studies also failed to establish a cause. Both patients recovered after arsenical therapy, and Irwin believes that intravenous injections gave much better results than did oral (carbasone) treatment.

Telles,[340] in Brazil, found in a child aged nineteen months the clinical, roentgenologic and hematologic aspects of tropical eosinophilia. Fever, failure to gain weight, cough with nocturnal paroxysms, and enlarged lymph nodes were present. Although eggs of Necator and Trichiuris were found in the feces, all symptoms and findings remained after treatment of the verminosis, but improvement followed intramuscular injections of arsenic. Another case is that of a European male who spent twelve years in Nigeria and returned to England. Six months later, according to Hunter,[174] nocturnal asthma began. He showed 12,400 white cells, with 59 per cent eosinophiles; his chest x-ray film was negative. Later, his count jumped to 36,200 white blood cells with 74 per cent eosinophiles. Three injections of novarsenobillon at weekly intervals led to rapid improvement in symptoms and to a normal blood count.

Another four articles come from India, the chief site of this condition. Jhatakia,[188] in an execellent paper, points out the freqency in India, especially in Bombay. He has seen 200 cases in the past eighteen months. The etiology remains obscure (allergic? parasitic? virus? spirochetal?). Many of his patients lived in grain centers or worked in grain shops. White blood cells varied from 10,000 to 90,000, and the percentage of eosinophiles from 15 to 92. The x-ray findings may be similiar to that in tuberculosis, and many show diffuse mottling. All findings clear when improvement occurs. Nair[249] is cautious. He says that the diagnosis of tropical eosinophilia can only be made with reservations, as pulmonary symptoms and blood eosinophilia can be due to various other known or unknown causes. The value of arsenic therapy as a "diagnostic test" is great, but not absolute; such therapy is also effective in other conditions. If filarial infection can cause eosinophilia and respiratory symptoms simulating tropical eosinophilia, as it did in one of Nair's patients who lived where filariae are prevalent, confusion in diagnosis can occur. Chauda[64] reports that a patient was markedly improved after six injections, 3 c.c. doses each, of acetylarsan (M & B).

Hall[151] favors the theory of infestation by mites as cause of this condition, and likes the term "pulmonary acariasis." One of his patients had never visited the tropics. Both had worked for many hours in hot, damp, and dusty store rooms. Hall points out that Engel (1935) described several cases of "privet asthma" with high blood eosinophilia long before Weingarten's articles. Carter and D'Abrera[59] also favor the mite theory. Various species of mites were found in the lungs or urine of twenty-five Ceylonese patients who had respiratory symptoms for three weeks to seven years, with prompt relief after arsenical therapy. The types of mites found in the sputum were essentially those commonly associated with store products, dust and debris; these mites are inhaled and the authors believe that they breed in the lungs or bronchi. These findings are similar to those reported in 1945 by Soysa and Jayawardena,[322] also in Ceylonese soldiers.

From the Netherlands West Indies, Van der Sar[357] also favors the mite theory. "Asthmatic bronchitis" was the chief complaint in four of eight patients; the other four had persistent cough without wheezing. Mites were found in the sputa of all, but repeated stool examinations for ova and parasites, and nightly blood examinations for microfilariae proved negative. Those who wheezed had from 58 to 80 per cent blood eosinophilia; of the four who did not wheeze, three had 14 to 18 per cent, and the other only 1 per cent. In five cases, x-ray showed pulmonary infiltrations characteristic of the "eosinophilis lung;" in two cases it suggested Loeffler's syndrome. In all cases treatment with Mafarside or Carbarson was successful, with no recurrences. Lavier's[209] paper is more or less a review, with a differential diagnosis from Loeffler's syndrome.

Probably the first autopsy report in tropical eosinophilia has just been reported by Viswanathan from Calcutta.[360] A twenty-eight-year-old man died of arsenical encephalopathy after the second injection of neoarsphenamine. Microscopic sections suggested an infective process rather than an anaphylactic reaction. The lesions are peribronchial, not perivascular. These findings suggest that infection in tropical eosinophilia is probably by inhalation. [This supports the "mite" theory.] The in-

fecting agent is thought to get into the peribronchial tissue and start inflammation which involves the interstitial tissue mainly, the alveoli partially. Discrete scattered areas of cellular infiltration, monocytic and eosinophilic, are produced. When the process becomes chronic, nodules containing giant cells and monocytes are formed; these areas are probably the cause of the disseminated mottled shadows seen in the x-ray films in tropical eosinophilia.

*Loeffler's syndrome* is also intriguing. Herbut and Kinser[161] gave horse serum intratracheally to sensitized rabbits. In a few minutes, cough developed, with sneezing, inspiratory dyspnea, and a rapid recovery; a few râles were noted in all animals. With each instillation of horse serum, respiratory symptoms were increased, and finally, anaphylactic death occurred in one rabbit. Slight leukocytosis was present. The x-ray showed transitory (but not migratory) pulmonary infiltrations which cleared in seven to thirteen days. The lung parenchyma revealed congestion, edema, eosinophilic pneumonia, and emphysema. The trachea and bronchi were also congested, edematous and infiltrated by eosinophiles. This picture is, therefore, like that reported by Schlect[351] in guinea pigs.

There are several reports in the human. Eichwald and Singletary[104] discuss a woman who had had a pelvic operation. Later she developed slight fever and vague symptoms and had 21 to 29 per cent blood eosinophilia. Her roentgen findings varied from a linear shadow interpreted as thickened pleura to rather an extensive irregular bilateral mottling which changed frequently. There was no response to antibiotics and no parasites were found. Alpher's first patient,[12] a chronic asthmatic who was sensitive to inhalants, had two and perhaps three attacks of Loeffler's syndrome; his other patient had ragweed hay fever when the syndrome developed. Alpher therefore suggests that the etiology of Loeffler's syndrome be divided into intrinsic (infectious) and extrinsic (pollens, drugs, et cetera).

A two-year-old boy, with a past history of "asthmatic bronchitis" and eczema, developed a septic type of fever for several months, together with severe anemia, leukocytosis, and persistent eosinophilia up to 84 per cent. X-ray showed pulmonary infiltration. The liver was large, and biopsy revealed focal necrosis. The child vomited an adult ascaris, and recovery was rapid though eosinophilia up to 34 per cent persisted.[261]

Sethna's patient,[311] from India, was wrongly diagnosed as a victim of pulmonary tuberculosis. Instead, he had a history of amebiasis, hookworm and ascariasis; he was allergic to the rays of the sun, had blood eosinophilia, and migratory and transitory consolidations on x-ray, and negative findings as regards tuberculosis. Sethna discusses Loeffler's syndrome in detail. Vaccarezza and Pavlovsky[353] report this syndrome in an allergic patient who developed urticaria, dyspnea and cyanosis after injections of gold salts. X-ray showed disseminated lesions, first of the nodular and then of the micronodular type.

Martinez[228] discusses all phases of the syndrome and has eight x-ray illustrations showing patchy infiltrations with clearing and recurrences. Wright and his associates[377] found that twenty-four (9 per cent) of 268 consecutive asthmatic patients admitted to the hospital at Camp Blanding, Florida, had x-ray evidence of pulmonary consolidation. Ten of these were diagnosed as of virus etiology because of fever and systemic symptoms. The remaining fourteen (5.3 per cent) were thought to have allergic consolidation, although they did not conform strictly to Loeffler's criteria, i.e., they did not have migratory infiltration and high blood eosinophilia. On the other hand, they were not typical of virus pneumonia because of absence of fever and systemic symptoms. They point out that mild cases of atypical virus pneumonia occurring in asthmatics can easily be confused with allergic consolidation. The same authors,[378] in a study of fifty-two cases of creeping eruption (cutaneous helminthiasis), found that twenty-six developed pulmonary lesions of the Loeffler type, with the usual paucity of systemic symptoms, but with blood eosinophilia. In 75.5 per cent of the cases, skin tests were positive for ascaris and trichina antigens, but examinations of the stools were negative for nematodes and ova, and no larvae were found in sputa. The pulmonary lesions in these twenty-six patients might be due to dead larvae in the lungs or to sensitization of the host to exotoxins elaborated by subepidermal larvae.

The subject of Loeffler's syndrome has evoked editorial comment,[79] with discussion of the role of allergy from extrinsic materials and as part of various clinical conditions. Autopsy reports have been very few to date and much remains to be learned.

*Periarteritis nodosa* has also attracted attention, both in the human being and in the experimental animal. Diaz-Rivera and Miller[92] found no etiologic agents in

seven patients who came to postmortem examination. Allergy was suggested as a factor in three, because of eosinophilia and migraine in one case and because of a rash in two others. The duration of symptoms was short and the onset acute, and the symptoms were so varied as to lead to frequent mistakes in diagnosis. In Goldsmith's case[143] the diagnosis was based on finding aneurismal dilatation of the inferior temporal artery on examination of the fundus in a patient who had received prolonged sulfonamide therapy. This is one of five cases in the literature in which fundus examination led to the correct diagnosis.

Higgins[165] presents six clinical cases with postmortem findings in one. The symptoms varied a great deal, as usual, depending on the organs involved and on the stage of the disease. Eosinophilia, if present, is of great aid as regards diagnosis; otherwise laboratory findings are not helpful. Periarteritis nodosa should be suspected in all patients with obscure and generalized symptoms.

Logue and Mullins[221] review the literature (177 cases): eosinophilia was found in 33 per cent, a history of allergy in 21 per cent. They believe that the etiology is diverse, perhaps due to sensitization to serum, drugs and infections. They add eleven cases, ages fifteen to sixty-five, with duration of illness from two and one half to twelve months. One patient recovered and was still well two years later. Hypertension was present in all at some stage of the disease, but there was no personal history of allergy, and none had received sulfonamides. Leukocytosis occurred in all, but eosinophilia in only five. An eleven-year-old boy developed periarteritis nodosa after the third week of scarlet fever, according to Peale and his associates.[259] There was a history of food allergy. Death was due to intracerebral hemorrhage and renal failure, and autopsy revealed vascular lesions in all organs.

Pettit[262] found very extensive pathologic changes at autopsy in a sixty-three-year-old female who was sick for eight years. She had fever, leukocytosis, albuminuria, hypertension, edema, and many other symptoms. The white blood count ranged from 7,300 to 62,000 with many monocytes; eosinophiles were never more than 3 per cent. Moschowitz[248] states that the clinical aspects of this condition result from three large clinical backgrounds, i.e., rheumatic fever, glomerulonephritis and malignant hypertension, plus the consequences of the widespread lesions which affect the circulation and the function of many organs. It can occur at any age, occasionally in infancy.

Miller and Daley[238] review the literature and add nine cases. Males predominate three to one; the disease is most common in the third decade; the average duration is six to twelve months; recovery may occur with little or no residual disability; any organ can be affected, but especially the kidneys; blood eosinophilia occurs in less than 20 per cent. The experimental evidence points to a reaction of hypersensitivity. The authors suggest that Loeffler's syndrome, Libman-Sacks disease, and lupus erythematosus represent localized forms of acute arteritis and are analogous in nature and etiology to periarteritis nodosa.

Bergstrand[28] discusses four patients, aged seventeen to forty-three, who died after illness ranging from six weeks to three years. All had manifestations of asthma, blood eosinophilia, severe diarrhea, hemoptysis and pleurisy. One also had painful joints. Autopsies revealed lesions typical of periarteritis nodosa in many organs, and also evidence of polyarthritis rheumatica. The lung changes were very similar to those described by von Mayenberg as characteristic of acute transient lung infiltration. Changes closely resembling those found in rheumatic pneumonia ("Frühinfiltrat" and rheumatic granulomas) were found. Bergstrand also believes the etiology can be extrinsic or intrinsic.

Thus we see that confusion still exists as regards tropical eosinophilia, Loeffler's syndrome and periarteritis nodosa. Each has its peculiarities but there is much in common; the differential diagnosis between them is not easy.

### ETIOLOGY OF ASTHMA

Inheritance in respiratory allergy has been studied by Stiles and Johnston.[328] In a family of five generations with 232 individuals, respiratory allergy occurred in 22.4 per cent in contrast with approximately 7 per cent in the general population. Perfect Mendelian ratios are not likely to be obtained in such a study, due to the complexity of both hereditary and environmental factors. The specific sensitivity is not inherited, merely the capacity to become allergic. Symptoms are influenced by the atopen, climate, degree of inheritance, age, sex, and other factors. Respiratory allergy may be of an irregular dominant character. The gene exhibits low penetrance with variable expressivity.

Cintra,[67] from Brazil, found that asthma and spasmodic rhinitis are hereditary in 68.02 per cent with the rhinitis occurring in only 5.48 per cent. There was a family

history of tuberculosis in 15.1 per cent, and almost every patient was sensitive to more than one substance.

Two reports come from Palestine. Melamed,[236] in a study of children under seven in the Sick Fund of the southeastern district of Tel-Aviv, found twenty-three cases of bronchial asthma and forty-six cases of asthmatic bronchitis in 1,400 children seen during the first year of the study. In the second year, 1,600 children under seven were seen, with thirty-seven cases of bronchial asthma and sixty-eight of asthmatic bronchitis. Asthma began in the first year of life in 5 to 6.5 per cent of cases, but most cases began between four and six. The majority of attacks were in September through November, the least in August. Statistics are not entirely accurate as in all surveys of this kind. Confusion exists because, as Glaser says, some authorities say that asthmatic bronchitis is a form of bronchial asthma.

Lass[208] states that allergic diseases are relatively more frequent in Palestine, probably because two-thirds of the population are immigrants who are exposed to new climatic conditions and new plants and substances. The actual incidence is unknown as many sufferers do not report for treatment. One-third of the population is cared for by a Sick Fund, and asthma in 1944 occurred in 0.98 per cent of those who reported sick (in England asthma occurs in about 0.6 per cent and in the United States in about 0.5 per cent). There are marked variations of surface contour, climate, soil and flora in Palestine, with 2,400 different varieties of flora. No season is free from blossoming. There is a variation in cities, with asthma (for six years prior to 1944) occurring in 0.42 per cent in Samaria to 2.11 per cent in Jerusalem. The incidence is lowest in rural districts and increases toward the shore line. The highest incidence of asthma occurred in children from one to thirteen (44.9 per cent). The incidence of allergic diseases is high and poses a serious social problem, especially among the poor in Tel-Aviv. The Sick Fund there has a large allergy clinic.

Pediatric allergy is stressed by Chobot,[65] but we dissent from his views that food sensitivity plus bacterial infection comprise the entire cause of asthma in the first few years of life. He states that when food sensitivity causes the asthma this sensitivity disappears spontaneously and the child has a free period until inhalant substances suddenly assume a major role. Bacterial infection is very important, and he therefore urges clean removal of tonsils and adenoids and the use of autogenous vaccines. [Our experience differs in that we rarely see that free interval, nor do we find foods the predominant cause of asthma at any age. Inhalants, we find, are the most important cause of asthma in infants, children and young adults. We do not deny the importance of bacterial infection, but removal of tonsils and adenoids, in our experience, has rarely led to cessation of attacks].

### HOUSE DUST

The importance of the *house dust antigen* is becoming more widely recognized, especially by those who test with potent extracts by both the scratch and intradermal methods. A strong positive scratch test to a good extract such as that made by Endo Products is almost always good evidence for clinical sensitivity. Those who still rely on the old-fashioned dust extracts which must be tested in strong dilutions and by the intradermal route are urged to do scratch tests with this extract. They will open their eyes in amazement and will not be so insistent on the importance of food allergy and infection, especially in children.

Efron[103] describes the usefulness of his purified dust extract, made according to the Boatner process and sold by Endo Products, Inc. Scratch tests are accurate in 90 per cent of the cases in which positive reactions occur; and in about 75 per cent of patients with asthma and/or allergic rhinitis, the scratch test with Endo dust is positive. Intracutaneous tests can be done but are unnecessary in most cases. This dust extract is dissolved in glycero-saline solution (50 per cent glycerin by volume), and dilutions are made with 0.4 per cent phenol in normal saline.

Oliveira Lima,[252] from Brazil, believes that house dust contains a specific antigen, not present in other indoor inhalants. In eleven atopic individuals (three with perennial rhinitis, two with bronchial asthma and six with both), six gave positive reactions only to house dust; the other five were also sensitive to foods but not to other inhalants. All tests were done intracutaneously, the dust in a 1:100 buffered saline solution. Passive transfer was positive for this dust extract in all eleven patients and entirely negative with the thirty-four inhalant extracts with which tests were also made.

Rockwell, Thomas, and Wittich[290] are to be commended for their report on standardization of house dust extracts. They headed a committee for the American College of Allergists, and for over a year they prepared and tested various dust extracts. Other members of the College collaborated in this work; members tested

the "unknown" extracts sent to them and submitted reports to Rockwell. From forty-eight different samples of house dust, twenty-four different extracts were made. A total of 365 patients were used for testing, and 3,224 individual tests were made, with controls. One interesting fact: no dust extract on the market, lot after lot, bottle after bottle, is exactly the same; for example, Rockwell tested two lots of Endo dust—one contained 0.409 mg. phosphotungstic acid precipitate, the other only 0.310.

The following conclusions were drawn: (1) No relation exists between skin reactivity and the total nitrogen. (2) Although some relationship exists between skin reactivity and the phosphotungstic acid precipitate nitrogen, it is not too good when there is appreciable variation in the molecular size of the dust antigen. (3) But when extracts were selected whose antigens were of approximately the same molecular size, and when they were adjusted so that the phosphotungstic acid precipitate nitrogen was constant, their skin reactions were alike within limits of experimental error. (4) Not much discrepancy existed in skin reactivity between extracts of dust collected in various parts of the country. (5) Extracts which were purified and concentrated with alpha picoline, or by the absorbed method, are potent, better than crude extracts or any other extracts which were compared. (6) Successful standardization can, therefore, be done by combining chemical and biologic methods. The total nitrogen and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate are determined. Such extracts should then be tested biologically and dilutions made based on their chemical analysis, namely, dilutions so that the extract contains 0.003 mg. phosphotungstic acid precipitate nitrogen per cubic centimeter. Such an extract should give positive reactions in a known dust-sensitive patient and negative reactions in normal individuals.

Brown and his co-workers[47] have a long and excellent review of the literature on the house dust antigen. The earlier results were at variance because the extracts were often very poor and skin testing was frequently associated with irritants. Therefore, passive transfer and constitutional reactions were infrequent. But since the work of Efron and his associates, a good reliable house dust extract is available, with excellent scratch test reactions in dust-sensitive patients, and with positive transfer and frequent constitutional reactions from injections. In other words, until a good dust extract was used, much of the earlier reports are not too important. Dust allergy is common and important, and, with avoidance and hyposensitization with good extracts, results are usually excellent. Barach[21] mentions dust hazard from concealed radiators; dust accumulates, and cleaning should be regular and thorough. Shambaugh[313] emphasizes the major role of house dust in causing chronic nasal and sinus symptoms, with superimposed infection; he obtains good results from injections of house dust extract. [We have noticed within recent years that some rhinologists have become overenthusiastic concerning the role of house dust. These workers should not forget that other allergens can and frequently do cause allergic rhinitis and sinusitis. In other words, tests should be carried out with all extracts which might possibly be factors, foods as well as inhalants.]

### FUNGUS ALLERGY

Deamer and Graham,[82] in a twelve-month survey of the atmosphere in San Francisco, found that Hormodendrum was the most common fungus; Alternaria spores were rare. Almost 60 per cent of the Petri-dish colonies were of the former, with only 2.4 per cent Alternaria; Penicillium colonies constituted over 19 per cent. There was no marked seasonal variation, and no great difference in plates exposed in the Marina residential district of San Francisco and those in Sacramento. This perennial character increases the difficulty in clinically detecting allergy to molds. Slides were also studied.

Reports also come from abroad. Nilsby[251] exposed plates for thirty minutes daily on the fourth floor of his home in Sweden from August to December, 1946. The greatest concentration of molds occurred at the end of August, decreasing during the defoliation period and increasing in misty weather. A few spores were present even in severe cold. Outdoors, Hormodendrum was the most common, followed by Penicillium, Pullarlaria and yeast-like fungi. Indoors, Penicillium was the leader and there were no seasonal fluctuations; colonies varied from 0 to more than 100 in one home. In another home, twenty-five colonies of Alternaria were found but this fungus is uncommon in Sweden. In other homes an almost pure culture of Monilia tropicalis was present. More fungi were found in rural communities than in the cities of Stockholm and Gothenburg. Spores were found in large numbers up to 200 meters, occasionally up to 700 meters (aeroplane studies). Very high counts occur in barns and threshing mills. Positive skin tests to mold

extracts were obtained in 15 per cent of 276 allergic patients (chiefly those with asthma and chronic rhinitis).

Duarte Silveira[96] lists nineteen molds and many bacteria found in the atmosphere of Rio de Janeiro. Hyde and Williams[176] caught Alternaria spores by the slide method in Cardiff, Wales. The total count from June to September, inclusive, was 646 (89 per cent of all spores) in 1942, and 726 (96.5 per cent) in 1943. The highest counts coincided with the highest temperatures. Very few spores occurred in late autumn or in winter. The source of the Alternaria spores is thought to be cereals growing in the vicinity. In 522 asthmatic patients in England, Fraenkel [120] found that 849 gave positive skin tests with extracts of Aspergillus, Penicillium or Mucor fungi. Molds are much more important in England than on the European continent, due to the excess moisture in England and to the construction of British homes. Sporotrichum, Cladosporium and Monilia are also frequent. A survey of the air in Barcelona, Spain, revealed Aspergillus, Penicillium, Cladosporium, and Alternaria as the most important molds, according to Frouchtman.[128]

Bieberdorf and Hampton[30] continued their studies of fungi in the San Antonio, Texas district, with special reference to skin tests. They found spores in the air almost daily, with high counts at intervals. Hormodendrum and Alternaria had the highest incidence by the plate method, Alternaria and Helminthosporium by slides. Significantly positive intradermal skin tests with mold extracts were found in 12.28 per cent of 186 patients; in thirty patients, mold extracts gave the only reactions. In 488 control individuals there were only six marked reactions with pseudopodia.

### POLLENOSIS

Jennes[187] counted ragweed at Waterbury, Connecticut. His counts were very low, being 393, 275, and 273 for the entire 1944, '45 and '46 seasons. Hyde and Williams[177] caught ten times as many grass pollens on slides which were placed vertically to catch the impact of the wind, as compared with those caught by the ordinary gravity method. There was little difference in counts between slides exposed on the roof of a building or on the ground in the midst of grass.

Despite positive scratch test reactions to pollen in 10.5 per cent of sixty-three Brazilian asthmatic patients, and in 13 per cent of sufferers from rhinitis, Oliveira Lima[254] has found only one undoubted case of hay fever, a Spanish woman. There have been no reports of true hay fever in native Brazilians. Three pollen seasons were found in a survey of twenty-four cities in Brazil: (a) a grass season from mid-May to mid-June (chiefly *Melinis minutiflora*); (b) *Ambrosia polystachya*, in San Paulo in October, November, and December; and (c) a cypress season in San Paulo and Curitaba.

Morton[246] surveyed Toowoomba, Australia, over a period of nine years. Asthma and hay fever from weeds is usually associated with sensitivity to grass pollen; tree pollen is of little importance. There is no true differentiation of seasonal allergy into early, middle or late summer types. Meteorologic conditions are very important and vary from year to year. Cypress pollen sensitivity in South Africa was important in fourteen cases of Ordman.[256]

### MISCELLANEOUS CAUSES OF ASTHMA

Finland furnishes two reports of asthma in bakers. Kilpinen[197] found eight cases of occupational "eczema" in 653 bakers in Helsingfors, and four bakers had occupational asthma and/or rhinitis. Linko[217] studied 328 workers at bread factories, bakeries and pastry shops who came in contact with flour; sixty-six were clinically allergic to flour (about 20 per cent). Asthma and rhinitis were found in twenty, asthma alone in six, rhinitis alone in forty. Eosinophilia in the blood was found in nineteen cases. Exposure tests were positive in forty-three of fifty trials. "Family predisposition" was not decisive as regards genesis of allergy to flour. Symptoms developed on an average within eleven years after beginning work in a bakery, but in thirty-two cases, signs appeared before ten years. [Our impression is that similar allergy in bakers in this country occurs more quickly.]

Gum tragacanth which was present in a brand of Pyribenzamine tablets led to asthma and urticaria in a hay fever patient of Brown and Crepea.[48] The Pyribenzamine and the other ingredients in the tablet were not responsible, as shown by feeding and by scratch tests. Scratch tests were positive for gum tragacanth and closely related 1 per cent karaya gum, and tests by passive transfer and by neutralization were positive for tragacanth and negative to both karaya and acacia. The patient had been excessively exposed to tragacanth while working in a candy manufacturing plant. The authors rightly observe that "before ascribing sensitivity reaction to the main ingredient of a medication, the other constituents also should be investigated."

Simon[317] notes the development of an allergen in wool. An eighteen-year-old boy had asthma for three years in the colder months, only at night, and only in his own home. He gave a 4-plus positive scratch test to an extract made from the comforter on his bed, with a negative control. Tests with wool from other sources, e.g., overcoat, glove, blanket and wool removed directly from a sheep, were all negative. The asthma ceased when the comforter was removed from the bed even though the patient continued to sleep in the same bed. [Perhaps a combination of mold and wool sensitivity may be responsible or an aging decomposition process.]

Friedlaender and Feinberg[124] found sensitivity to aspirin in forty-five chronic asthmatics (seventeen men and twenty-eight women). The onset of the asthma almost always preceded the discovery of the allergy to the drug. As expected in this type of asthmatics, chiefly middle-aged, skin tests were only positive in sixteen patients, with clinical improvement in only twelve of these. Eosinophilia, emphysema and nasal allergy with polyposis were commonly associated. The authors suggest that these aspirin-sensitive patients might also be allergic to some other simple chemical compound with resultant symptoms. "Such a mechanism could explain the many cases of allergic disease in which a specific protein allergen cannot be identified."

Other chemicals have been incriminated. Sulfathiazole powder caused typical asthma by inhalation in two nurses, as reported by Rosberg.[291] Epicutaneous tests with sulfathiazole were negative, but positive reactions were obtained with 2-aminothiazole hydrochloride (in both cases) and acetylsulfanilchloride (in one case), substances probably formed by the decomposition of sulfathiazole in the body.

In ten asthmatic workers in the fur industry, Silverberg and Heimann[315] hold paraphenyldiamine (fur dye) responsible. Scratch tests with the dye were negative in all ten, but four gave positive reactions on patch testing with the dye (only one of these had a dermatitis). Patch tests on workers who had neither asthma nor dermatitis were negative. Here, then, is a paradoxical situation in that the shock tissue which reacted (epidermis) is not the one which reacted clinically.

Jamieson reports two cases also apparently due to chemicals. One patient, a provincial apiarist, developed asthma from bee scent,[184] and severe asthma developed within a minute after inhaling from a vial which contained bee scent dissolved in ether (three negative control vials of ether). He also gave positive skin and passive transfer reactions to an extract of bee wings, but when this extract was washed with acetone, skin tests were negative. Contents of the bee scent glands dissolved in buffer solution gave a marked positive reaction. This patient gave positive skin reactions to all members of the super-family of the *Apoidea,* but to no other members of the super-family of *Hymenoptera.*

A twenty-seven-year-old housewife[185] wheezed and coughed when changing wet diapers or washing them. Attacks always began in about two minutes and lasted about thirty minutes. The attacks were more severe if a stool was mixed with the urine. The patient also had asthma from flatus, heavy perspiration, Limberger and green cheeses, rotting seaweed and skunk odor. The family history was negative for allergy. By inhalation experiments, Jamieson proved that the attacks were due to the ethereal sulfates, the aromatic end products of protein metabolism as excreted in urine, feces, and sweat. The attacks from cheese are due to the acid formed by the proprionic bacteria present in these foods.

Ordman, from South Africa,[257] reports thirteen cases of bronchial asthma due to inhalation of the dust resulting from the disintegration of the bodies of sewage filter flies (Psychoda). All patients worked at a sewage plant in the Transvaal. One case history is given in excellent style, including a strongly positive passive transfer reaction. In six cases, skin tests were positive, and in three of five, passive transfer was also positive. Control tests were negative in twelve non-asthmatic individuals. From East Africa, Reed[280] reports severe asthma and urticaria in a European who had been stung by a bee three minutes previously, with relief from asthma by epinephrin. Cattaneo and Alberici[60] report asthma for ten years in an Argentine woman, with associated urticaria, cephalgia and pains of the gall-bladder-colic type. Positive reactions for hydatid disease were found, along with 11.6 per cent blood eosinophilia and eosinophilia in the sputum, and with Charcot-Leyden crystals and Curschmann spirals. X-ray revealed a calcifying hydatid cyst of the liver. The patient was given the treatment of Calcagno: intramuscular injections of fresh human hydatid fluid, beginning with 0.50 c.c., increasing 0.25 c.c. every three days, with maximum dose of 7.0 c.c. and a total of 62.0 c.c., without notable reactions. The asthmatoid symptoms disappeared, and she was still symptom-free ten months later.

The factors which contribute to attacks of asthma, e.g., psychogenic and endocrine, will be discussed in the section on treatment (q.v.).

### PATHOGENSIS AND PATHOLOGY OF ASTHMA

A death from asthma[83] occurred in a boy aged twenty-two months. He was first seen at eleven months with "asthmatic bronchitis" which followed an upper respiratory infection two months before. He had had persistent rhinitis and an intermittent cough since the onset. The child was released from the Children's Memorial Hospital, Chicago, and readmitted a month later for bronchoscopic examination, with normal findings. At fifteen months the diagnosis was changed to bronchial asthma; skin tests were negative. They were repeated three months later by one of us (L.U.), and again all tests, including all dilutions of house dust, scratch and intradermal, were negative. Asthma continued despite a trip south, and he received many injections of epinephrine. His final admission followed rhinitis; terrific asthma ensued, with no relief from aminophylline, glucose, epinephrine, et cetera. Temperature rose to 107.2° F., with marked cyanosis, numerous wheezes, rhonchi, and death. Autopsy showed 100 to 150 c.c. of sterile fluid of unknown origin in each pleural cavity, with all branches of bronchi occluded by thick light green, tenacious mucus which by smears showed many eosinophiles; B. coli was isolated. Final anatomic diagnosis included: (1) marked mucopurulent bronchitis and bronchiolitis, (2) asthma (clinical), (3) bilateral hemothorax, (4) foci atelectasis, (5) compensatory emphysema, and (6) foci of pulmonary edema. As Unger suggested in his discussion of this case, the child might possibly have been helped by bronchoscopy in his terminal illness, but his condition when seen seemed too critical for even this procedure. [We have recently relieved coma twice in an elderly asthmatic patient who was too feeble to cough up her sticky sputum. Bronchoscopic aspiration was life-saving here, as it often is in other patients of this type.]

Lowance and his co-workers[225] present seven cases in which death in asthma was thought to be complicated by or caused by cardiac complications. Autopsy was done in one case, in which a thirty-eight-year-old patient with hay fever, asthma, positive skin tests and positive family history for allergy died in a doctor's office. The main findings were acute dilatation of the right side of the heart, marked emphysema, old pleural adhesion, and cholelithiasis. The pathologist said the patient died of right heart failure, plus active severe generalized emphysema. The heart was quite small, and the lungs bulged. No electrocardiogram had been done.

Autopsies were not done in the other six cases. Patient *2*, aged twenty-nine, with asthma for two years and marked sinus and nasal involvement, and with repeated hospitalization, died in status asthmaticus. Patient *3*, aged seventy-two had "asthma" plus cardiac decompensation, with negative skin tests. These cases and the others noted were believed to have cardiac complications in allergic asthma.

Love and Driscoll[224] injected 100 million anti-typhoid organisms intravenously in a twenty-year-old man with choroiditis. The temperature rose to 102° in twelve hours and was normal in three hours. A second dose (same strength) was given the next day; in one hour the temperature was 102.6° and rose to 107.2° F., with chill, tachycardia, vomiting of bloody material, hematuria, and a blood urea nitrogen up to 66 mg. Death occurred on the next day. Autopsy revealed generalized petechiae in the brain and parenchymal organs and massive necrosis of the liver and kidneys. Death was thought due to a generalized anaphylactoid reaction similar to that described by Sanarelli and Shwartzman in experimental animals. The authors believe that the unfortunate reaction could have been avoided if the interval between intravenous injections had been lengthened to forty-eight hours or more.

One of us (L.U.) has also recently had a similar unfortunate experience. The first dose of typhoid vaccine (10 million) was injected intravenously on the same day to three patients who were in the hospital for status asthmaticus. Two responded favorably with the usual chill, low fever, and temporary improvement in asthma. The third patient, a woman aged fifty-five, developed a chill, a higher fever than the others, diarrhea, collapse, and rather sudden death. Autopsy was urged but was refused. This is our first fatality with this procedure. There was no previous known typhoid fever nor injection of typhoid vaccine.

Death has followed injections of thiamine hydrochloride. Reingold and Webb[281] had given three large intravenous injections without serious reaction, but the fourth dose of the same strength led, within ten minutes, to generalized burning, profuse perspiration, dyspnea, cyanosis, and death. Autopsy showed constriction of the pulmonary arteries with engorgement of the lungs, right heart dilatation and failure, and mild emphysema. Death was thought due to allergy to thiamine. Sundelin[320]

injected a thiamine preparation called Aneurin. The seventh intramuscular injection in his forty-year-old patient was followed by coma, wheezing, dyspnea, thready pulse, urticaria, diarrhea and vomiting, with recovery after a few days.

A death which may or may not have been associated with periarteritis nodosa is reported by Hill and Damiani.[166] Death occurred twenty-five days after inhalation of a spray containing a 6 per cent solution of DDT in kerosene. Marked asthmatoid symptoms occurred, with progressively increasing dyspnea and cough with temporary relief from frequent injections of epinephrine. A severe generalized, pruritic, maculopapular rash was also present. There were 43,000 white blood cells with 20 per cent eosinophiles. Biopsy and autopsy findings suggested periarteritis nodosa.

Rifkin's twenty-four-year-old soldier was given 1.0 c.c. of typhus vaccine subcutaneously.[285] Sudden dyspnea occurred, with death within twelve minutes. There was no previous injection of typhus vaccine, but records did indicate sensitivity to egg. Autopsy revealed severe emphysema, marked eosinophilia in the bronchial secretion and the walls of the bronchi and bronchioles. The findings were attributed to tetanic contraction of the bronchial muscles with resultant emphysema and eventual asphyxia. Ratner and Untracht[276] have an excellent paper on allergy to Influenza A and B vaccine in children. In a group of 108 highly allergic children, 10.2 per cent were sensitive to egg white protein, but only 4.6 per cent were sufficiently allergic to cause alarm as regards injection of influenza vaccine. All persons should be tested intradermally with undiluted vaccine, using 0.02 c.c. before administering each and every dosage; if this test is negative or suggestive the vaccine can be given with impunity. A history of egg-sensitivity is not as reliable a criterion as is the intradermal test with the vaccine, say the authors.

Ahroon[8] reports death after a second local application of 2 per cent Pontocaine prior to bronchoscopy, with the first application ten days previously. Pontocaine has fifteen times the anesthetic power of cocaine and is two and one-half times as toxic. There is no known test to reveal sensitivity, and reactions seem to occur more often in allergic individuals.

Selle[308] discusses the physiologic basis of asthma. No one has actually seen bronchospasm through a bronchoscope but, of course, the terminal bronchi are not accessible to direct observation. Thickening of bronchial muscles does occur in some cases, but he favors the theory of occlusion by plugs of tough sticky mucus as commonly observed by such men as Rackemann and Unger. While there is much evidence to substantiate the histamine concept, it is a fact that the so-called antihistaminic drugs like Benadryl are of little use in asthma.

Selye[309] has a very lengthy paper on the "General Adaptation Syndrome and the Diseases of Adaptation," with a tremendous bibliography. He is an earnest and enthusiastic worker, and we can all learn much from him. His alarm reaction is defined as "The sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted." The reader is urged to study his entire article.

An interesting note comes from an answer to a query in England.[6] There is no evidence that production of adrenaline is deficient in asthma, and the absence of signs of lessened sympathetic activity supports the view that there is probably no type of asthma caused by deficiency in secretion of adrenaline. The asthmatic reveals no pathologic changes in his adrenals. It is possible that psychologic factors which precipitate asthma may cause parasympathetic overaction and thus cause attacks. It has been noted, for example, that during conditions of prolonged fear in London, as in air raids, asthmatic patients have *not* had attacks in circumstances where attacks were expected.

H. Miller[239] of Los Angeles, in discussing the physiological basis for treatment of intractable asthma, points out that bronchial asthma is a proof of bronchial obstruction, regardless of the cause, and the most common causes are allergy and infection. The obstruction produced by the defense mechanism is due to bronchospasm, mucus plugging, and bronchial edema, and treatment must be based on a proper appreciation of each of these possibilities. [We would place bronchospasm as the third rather than the first factor.]

From France, Anglade[14] discusses voluntary apnea in normal and asthmatic children. The longer the child can hold his breath, the more nearly normal is the child. When there is diminution of voluntary apnea, another attack of asthma will probably take place in a few days. This method is excellent in noting improvement or lack of improvement.

Robinson[289] has a long article on "Stagnation of Tissue Fluid Is a Constant Pathologic Finding in Allergic Disease of the Nose and Paranasal Sinuses." Removal of this excess fluid by local pressure, as by balloons, tends to prevent nasal polyposis

and thus aids in preventing or relieving some cases of bronchial asthma which are related to sinus disease. The duration of relief varies.

Rackemann philosophically discusses some future problems in allergy.[273] Asthma which begins after the age of fifty-five is not the conventional asthma which starts in childhood. Allergy is not an important factor in the former group, but if an older individual has had asthma for many years, she or he is just as allergic as a youngster and needs and deserves the same care in skin testing and injecting as is given the younger patient. This plea followed the report of death from skin testing in a seventy-eight-year-old patient who had asthma since the age of four. Intracutaneous tests were done without preliminary scratch tests.[374] [We have pounded on this point over and over again, yet conversation with physicians from all over the world reveals an alarming proportion who still do nothing but intracutaneous tests; a few more do some, but not complete, preliminary scratch tests. Along this line, the wholesale selling of sets for intradermal testing is dangerous and to be deplored.]

Confirmation of our point of view comes from Swineford.[336] A man aged forty-nine, with asthma for four years, gave a history of distension and burning from mustard, catsup, mayonnaise and cabbage, and of asthma and rhinitis from inhalation of hay, feeds, grains and house dust. Preliminary scratch tests with seventy-two commonly reacting allergens proved negative. Then intradermal tests were done with fifty-six foods and eight or nine inhalant extracts; the patient became ill and, despite heroic treatment, died within fifteen minutes. The skin tests showed very little because the man died very quickly. Autopsy was not done. In the second case, a woman, aged forty-nine, with asthma for fifteen years, had the asthma following onions, tomatoes and mustard and inhalation of several inhalants. Seventy-two preliminary scratch tests were also negative. Then about sixty-five intradermal tests were made, and thickness of the tongue, asthma, apprehension and delirium occurred quickly. Fortunately, large doses of epinephrine and aminophylline, followed by hospitalization, were successful. Later, scratch tests were done for all the injected food extracts, and a huge reaction occurred with the mustard-turnip-water cress group; the patient then recalled severe asthma and rash from mustard. No preliminary scratch tests to mustard had been made. The previous patient was the first fatality observed by Swineford in 7,000 patients who had been given intracutaneous tests after a preliminary set of seventy-two scratch tests. The author concludes: "Every intradermal test should be preceded by the less sensitive scratch test."

Harkavy[155] continues his writings on vascular allergy which were previously summarized.[349] Sensitivity to foods, pollens, sera, drugs, and bacteria may give various degrees of hyperergic reactions in the cardiovascular system. These changes are reversible at first if the offending agent is removed or corrected. Irreversible reactions, especially in the heart or kidneys, cause fatal cardiac or renal failure, as in seven of sixteen patients studied.

"A patient with long-standing asthma is under my care and contemplates a trip from Ohio to California. Would traveling in an airplane be harmful to him? Would the high altitude affect him in any way?" The answer to this query is excellent: "Asthma is not caused by anoxia nor is the usual attack of asthma associated with anoxemia. The latter phenomenon is discernible only in the severe stages of status asthmaticus. On the other hand, the high altitudes, owing in part to lesser amounts of airborne allergenic and nonallergenic irritants, lesser humidity and other conditions less easily understood, frequently improve the asthma. Unless the patient has cardiac decompensation, the altitude should not harm him."[272] [None of our patients has been harmed by high-altitude flights.]

Jacobs[181] cites experimental evidence regarding the importance of cilia in raising mucus; in fatal cases of bronchial asthma, an increase in goblet cells is frequent; this increase, plus damage to the cilia, leads to an excess of mucus difficult to raise. These factors, plus an upper respiratory infection which may destroy cilia, may lead to increased secretion and sufficient narrowing of the lumina to cause wheezing. Correct treatment of the infections, plus the use of potassium iodide to loosen the mucus, plus avoidance of narcotics, usually suffices to end the attack of asthma. Whooping cough, measles, and influenza can also damage the upper respiratory tract, especially in children, to an extent sufficient to cause outright asthma in a child who has a subclinical allergy.

In an excellent article, well illustrated, on pathology of asthma, Jiménez-Diaz and his associates[189] conclude that the obstruction is not due to bronchospasm. Rather it is essentially an acute congestion of the lungs with *ingurgitation* of the smaller circle through venous closing of the exit. In shock, by means of air, and in general, in slow shock, the congestive phase leads the way to another phase with arterial contraction and interstitial edema. Both the congestion and edema suffice to dilate

and hold rigid the alveoli. Attacks of bronchial and cardiac asthma are produced by the same mechanism, vascular or edematous ingurgitation, though the means differ. The best drugs, then, empty the smaller circle and suppress the edema.

Graña's article on "Hydatid Allergy"[148] is interesting. Some patients with hydatid cysts have asthma; others may have urticaria or angioneurotic edema (besides their nonallergic symptoms). He describes the Casoni and Pontano reactions, and notes blood eosinophilia up to 25 per cent in patients with cysts. If such patients receive injections of 1.0 c.c. hydatid fluid, a great increase in blood eosinophilia occurs in twenty-four to forty-eight hours. Typical crises of asthma occur in these cases, with benefit either from extirpation of the lung or liver cyst or desensitization with the hydatid fluid itself. Rupture of cysts may lead to anaphylactoid symptoms but "histamine apparently is not concerned with this type of shock."

### SYMPTOMATOLOGY OF ASTHMA

Tuft[347] has reviewed the subject of bronchial asthma from various aspects, including the gradual change which occurs in many cases from intermittent to chronic. He points out the frequent association of nasal allergy, and decries the wholesale surgery of the nose and sinuses which is now, happily, becoming a past epic. He, likes us, dislikes the terms "intrinsic," "infectious," or "bacterial" as applied to asthma. He prefers to call them all allergic so that there will be an incentive to search for a possible etiologic factor. He likes the term "idiopathic." Old age is no bar to real allergy. A patient can be sensitive to foods, inhalants, and perhaps even bacteria in old age as in children. Better results in old age come from treatment based on the allergic point of view.

But Rackemann[274] still prefers the terms "extrinsic" and "intrinsic." He divides intrinsic asthma into six groups:

1. Asthmatic bronchitis, which may occur with "colds," and these patients may also be allergic to some extrinsic factor, e.g., dog or egg. Treatment must be directed against both the infectious and allergic elements.
2. Vasomotor rhinitis, with negative skin tests, often in young adults, and often followed by severe asthma.
3. Bacterial allergy in older group of asthmatics. Environment and foods are not factors.
4. Depletion, when asthma is complicated by somatic factors, e.g., loss of weight and exhaustion, and by psychic factors, e.g., loss of morale.
5. Polypoid sinusitis with asthma. The nasal lesions are part of the picture, not the cause of the asthma.
6. Emphysema is a part of every attack of asthma but in the acute process is reversible. The chronic becomes irreversible.

Waldbott[362] asks "Is there an Intrinsic Asthma?" His answer is *no*. In a survey of 323 chronic asthmatics in 1,442 cases of asthma seen from 1942 to 1945, he was unable to see any real differences between this group and the rest of the asthmatics except that symptoms were chronic. It is true that "intrinsic" causes were responsible for attacks in many of these 323 patients, with influences such as sensitivity to cold, endocrine products (premenstrual aggravation), bacterial infection, and psychogenic factors. But "in no case were such intrinsic factors found to be the only causes to the exclusion of those termed extrinsic. The evidence indicates that there is no justification for the diagnosis of intrinsic asthma as a symptom-complex, and that the concept of such a syndrome may lead to faulty diagnosis and to abandonment of treatment at a time when treatment is needed and may be most effective."

We particularly like Waldbott's statement that "the most significant point brought out by Cohen (who favors the term 'intrinsic') is the utter hopelessness with which he views the existence of intrinsic asthma. He (Cohen) speaks of the waste of the physician's time and the patient's money if intrinsic asthma is not recognized. Such a conception (says Waldbott) is actually shared by many, perhaps by most, leading allergists. It cannot fail to have serious consequences. Indeed, I have seen patients in whom treatment has been abandoned because their asthma was defined by the physician as 'intrinsic.' Such an attitude by the physician necessarily creates a great deal of despondency on the part of the patient." [We may add that thorough skin-testing by both the scratch and intradermal methods will decrease the number of "non-reactors"; and a thorough history and examination will uncover some referred as asthmatics but who have other conditions, e.g., carcinoma.]

Hedström[159] discusses 1,250 asthmatic patients whom he has observed at the Äre

Mt. Sanitarium from 1923 to 1944. He recognizes the complex nature of asthma—an excellent paper, especially as regards handling of psychosomatic angles. Banchieri[19] discusses a case of bronchial asthma and divides the cases into those due to inhalation, to ingestion and those induced, as by overdose of antigen or by serum therapy.

There are three papers on vital capacity. Brown[49] and his co-workers studied forty-two hay fever patients over a period of two years; eighteen of these had simple ragweed hay fever, while the rest either had asthma or were sensitive to ragweed and other allergens. Vital capacity readings were made before and after August 11, chosen as the start of the ragweed season. Results: uncomplicated ragweed hay fever patients frequently show a lessened vital capacity during the season and most of these derive little benefit from injections of pollen extract. Variations in capacity are greater in those with multiple sensitivities. Intercurrent respiratory infections lower capacity, and pollen asthmatics have a lowered vital capacity even when they do not have clinical asthma.

Lowell and Schiller[226] did what Blackley tried on himself some eighty years ago [a rather dangerous experiment and not one to be recommended for general use]. Reduction in vital capacity to as little as 60 per cent of the original figure was obtained in each of six asthmatic patients who inhaled aerosolized extracts of birch, oak, grass and ragweed pollens. Cough, contriction of the chest, dyspnea, wheezing and hay fever occurred, as would be expected. The greater the asthma, the less the vital capacity. In all patients except one, the vital capacity returned to the control value within fifteen minutes, and the maximum degree of depression occurred six to ten minutes after inhalation.

Loeb[218] has an excellent article on physio-pathology in bronchial asthma. He gives thumbnail explanations of total lung capacity, ventilatory capacity, et cetera. His findings of abnormal respiratory patterns in asthmatic patients between attacks, in well-controlled experiments, are enlightening. He pleads for better understanding of allergy by the internist and for better knowledge in internal medicine by the allergist [Amen].

Asthma in children has not been neglected. Schwartz[303] stresses the importance of chronologic records in the management of allergic children. He devised a chart to indicate the occurrence of symptoms, the time of onset, frequency of attacks, location of symptoms, and possible changes in shock organs. In a boarding school, for example, a pupil whose symptoms occur December 21, March 28 and June 12 and who improves on returning to school is 'almost certainly allergic to something in his own home (pet?). Records are more dependable than memory.

Ratner[277] points out that asthma rarely begins before the age of three to eight, but frequent bouts of rhinitis usually precede the asthma. A careful history is very important; fever can occur in simple asthma but care must be taken to exclude infectious processes; skin tests should not be done until about a year has passed [we advise skin tests as soon as possible]. Scratch tests should always precede intradermal, and multiple sensitivity is the rule. Food sensitivity is not as important as inhalant (opposite to views of Chobot).

A questionnaire was sent to 338 children who had been hospitalized for bronchial asthma from 1926 to 1939. Replies were received by Flensborg[117] from 298 of these children, of whom 63 per cent were males. In 66.4 per cent the onset had occurred before the age of five, chiefly in the second and third years; in twenty the onset was during the first year, and asthma persisted. If "bronchitis" can be accepted as the criterion of onset of asthma, the average age of onset is considerably earlier. Replies showed that the attacks of asthma ceased in 40 per cent and recurred in 56 per cent. Death occurred in fifteen children (5 per cent), with status asthmaticus in five. No asthma was present in 41 per cent of the 131 children who reached the age of eighteen, and in 46 per cent of the 166 who had become twenty years old. Change in environment was the most important factor in clearing the asthma. But even in those who no longer had asthma, dyspnea on exertion was present in 44 per cent.

In England, where skin tests are much less thought of, and in fact, often laughed at or ignored, the results of skin tests are naturally disappointing. For example, Fisher[114] states that skin tests were practically negative, especially for inhalants and milk, in 200 children, of whom 48 per cent developed asthma in infancy, with onset in another 39 per cent between the ages of two and six. Respiratory infections, especially measles and whooping cough, frequently precede the onset, and it is often difficult, at first, to separate infectious symptoms from true allergic bronchial asthma. [A physician from India visited us recently. He said that he saw very little skin testing while he was in Great Britain and that practically none is done in India. We will gladly demonstrate patients and skin tests to visitors.]

Rittwagen and his associates,[288] in a study of 100 children with rheumatic fever and 100 non-rheumatic children, report 33 per cent positive personal history and 31 per cent positive family history for allergy in the rheumatic group, and only 8 and 10 per cent, respectively, in the controls. Asthma occurred in 5 per cent of the rheumatic children, with hay fever in 2 per cent, food allergy in 12 per cent, and allergic rhinitis in 10 per cent.

Forman[119] courageously writes of asthma in the older group. Some are non-atopic, but he considers all as allergic until otherwise proved. His principles of treatment are in the section on treatment. [It is heartening to know that there are men who do not give up when elderly asthmatics are placed under their care. Much can be done.]

Brunn and Lons,[52] from Norway, have confirmed our belief that hyposensitization with specific allergens diminishes the size of skin test reactions, and that clinical improvement goes hand in hand with this lessening in the size of the skin tests. They did intradermal tests in seven different concentrations from 1:10,000 to 1:100 in 150 asthmatics. After hyposensitization, skin reactivity was diminished in 78 per cent, unchanged in 20 per cent, increased in 2 per cent.

Changes in the electrocardiogram during allergic shock are described by Castberg and Schwartz.[62] In animal anaphylaxis, changes in heart function are due to myocardial anoxia, not to allergic changes in the myocardium. In five hay-fever patients in whom constitutional reactions were occurring, with dyspnea (epinephrine withheld), tracings were similar: tachycardia, $P_2$ increased, R 1 and R 2 decreased, T wave flattened in Leads I and II. In one case a positive T 3 became negative. In three cases the S-T segment was depressed in Lead II. The P-Q, QRS and QT intervals showed very little change. These changes are typically found in experimental oxygen deficiency tests. A very low pulse during shock may be due to a vagus effect and may cause death unless 2 mg. of atropine are injected intravenously.

Heyer[163] reports as follows: (1) Pneumographic tracings of respiration revealed a similar type of distortion and prolongation of the expiratory phase in cardiac patients with pulmonary congestion and in patients with allergic asthma. Expiration in these patients did not undergo the relative shortening seen in normal persons. (2) During intravenous administration of aminophylline, the expiratory phase of patients with heart disease and asthma was promptly shortened, along with an abrupt and considerable increase in vital capacity. (3) The authors suggest that these changes in cardiac patients may be due to reflex bronchospasm induced by pulmonary congestion.

Asthmatics are subject to many complications, some serious. *Febrile conditions* are very common, and these include acute and chronic bronchitis, various types of pneumonia, and sinusitis, as well as other feverish conditions common to all individuals. Sodeman and Derbes,[320] in discussing the febrile asthmatic, state that the fever may be due to any one of the following: status asthmaticus with lung changes which they term "allergic bronchopneumonia"; Loeffler's syndrome; tropical eosinophilia; bacterial bronchitis; peribronchial pneumonitis; bronchostenosis; fever from the therapy itself (e.g., injections of pollens, room inhalants, vaccines), and various intrathoracic diseases (e.g., tuberculosis and carcinoma).

*Emphysema,* which probably occurs in all chronic asthmatics, is discussed by Kahn, [191] who notes that treatment must be directed at the emphysema itself as well as the underlying asthma. Many of these patients are oversensitive and demand extra care as regards injections. Skin tests are frequently negative, yet, clinically, many of these patients are allergic to pollens and house dust and may obtain good results from hyposensitization. Such patients are not "intrinsic" or "infectious." Allergic rhinitis, sinusitis, and nasal polyposis are frequently associated. Polyps should be removed, but best results come from treating these patients meticulously from the allergy point of view. Kahn urges rest of the overworked lung, rest which should continue until exertion causes no dyspnea; this may require months, and is best carried out in the hospital at first, later at home. With this prolonged rest, as with chronic tuberculosis, gratifying results are obtained. Avoidance of allergenic factors as by filters, is important during this rest period. Kahn urges long rest periods after every attack of asthma; this will tend to prevent the onset of emphysema. Complete recovery after emphysema is well established cannot be expected.

Death due to *spontaneous pneumothorax* in a patient with chronic asthma is reported by Castleman.[61] Pneumothorax can also occur in tuberculosis, and in nontuberculous and nonallergic individuals. Lombardi[222] reports such a case in an infant with subpleural blebs leading to multiseptate benign spontaneous pneumothorax.

*Subcutaneous* and/or *mediastinal emphysema* is comparatively rare; it can be caused by bronchial asthma or can occur independently. In children, Glaser states that only seven cases were reported up to 1941 as occurring in asthmatic children under ten. Larguia and Sojo[207] report subcutaneous and mediastinal emphysema which occurred in an eleven-year-old child during an attack of asthma. Precordial pain and dysphagia were prominent, and relief followed the use of morphine and codeine. The child also had tuberculosis [this means that the rupture may have been related either to asthma or to tuberculosis.] Another case occurred in an asthmatic five-year-old girl, as reported by the Children's Memorial Hospital, Chicago.[235] The child had been diagnosed as virus pneumonia, but the correct diagnosis was evident when typical crunching, bubbling sounds were heard over the precordium during cardiac contractions. This excellent paper also points out that x-ray characteristically shows elevation of the mediastinal pleura from the mediastinum and pericardium, producing a unique line on one or both sides of the mediastinal shadow. On the left this line is commonly visible above the pulmonary vessels and is due to the escape of air from the ruptured alveoli; the air travels along the vessels into the mediastinum. It is occasionally necessary to release air from the mediastinum (needle puncture, dissection through the neck, or splitting the sternum), but recovery usually occurs spontaneously. Crepitation, when and if the air reaches the neck, is, of course, diagnostic.

Schwartz and his associates[304] also discuss acute mediastinal emphysema. In excellent style, they report one case which occurred during an attack of asthma and hay fever, and six others which apparently were of spontaneous origin. They emphasize the typical crunching sound due to the thrust of the heart against air bubbles; this sound can often be better heard if the patient bends forward or lies on the left side. Five patients experienced a recurrence, and in two of these there were prolonged symptoms over six to nine months. All six spontaneous cases (not the asthmatic) had an associated spontaneous pneumothorax. They emphasize the necessity for careful examination of the precordium for mediastinal emphysema in all cases of spontaneous pneumothorax, especially if there is a small left apical pneumothorax. The best treatment is prolonged rest.

Van der Laan and Maresh[356] also report mediastinal and subcutaneous emphysema. A nineteen-year-old girl had such a severe attack that relief was only obtained after a "7.6 cm., low collar incision was made just above the sternal notch (local anesthesia). The muscles were separated in the midline, and a finger was inserted into the superior mediastinum through the suprasternal notch. There was an egress of air, and rapid improvement in the status of the patient followed. The subcutaneous emphysema disappeared gradually, and convalescence was uneventful." But their other patient was not so fortunate. A similar surgical procedure was necessary, but, despite some egress of air, death occurred nine hours after the operation and forty-eight hours after onset of symptoms. Autopsy revealed a "longitudinal linear rupture of the esophagus, 2 cm. long, just above the esophageal hiatus of the diaphragm." It communicated with a collection of foul fluid. The tear had evidently occurred in the course of marked vomiting and retching following consumption of a large amount of alcoholic beverages by the fifty-eight-year-old patient.

The relationship between bronchial asthma and *bronchiectasis* is not clear. The two can occur together, possibly independently. An asthmatic thirty-five-year-old man has been under the care of one of us (L.U.) for several years. He also had a very severe bronchiectasis of the left lower lobe, with some involvement of the right lower lobe, and with frequent bouts of pneumonia and pneumonitis. Since his left lower lobe was removed in May, 1946, his improvement has been remarkable. He still has occasional mild hay fever and asthma and is receiving appropriate injections, et cetera; but he has gained about thirty pounds, has had no further febrile attacks, and the râles which were present in the right lower lobe have disappeared. Lobectomy is by far the best treatment for bronchiectasis, if the patient is a fairly good surgical risk and if one has available an experienced chest surgeon. The condition can occur at any age, even in childhood. Diaz-Nielson[91] reports a case, proved by bronchography, in a six-year-old boy, ill for three years following pneumonia. Cough and expectoration are the main symptoms. [Operation was not done, apparently, but should be carried out.]

Recurrent allergic parotitis, a rare complication, is reported in three asthmatics by Waldbott and Shea.[363] The swellings usually occurred just before onset of attacks of asthma. In one patient, swellings preceded the initial onset of asthma. Elimination of causative foods resulted in relief from swellings; therefore, recurrent parotitis may be alleregic.

### DIRECT DIAGNOSIS OF ASTHMA

Bronchial asthma is a condition rather easily diagnosed in most cases. Very little new material has appeared, and these chiefly on refinements and aids in diagnosis. For example, Dutton does not like Wright or Giemsa stains in examination of nasal and sputum smears.[99] He prefers eosin followed by alcohol acetone, then methylene blue—the whole procedure in about thirty seconds. The eosinophilic granules stain an intense pink, all other elements blue. Slides should be examined under low power first, else one may miss scattered patches of eosinophilic cells. Dutton[99] also suggests a rapid darkfield technique for examining sputum for bronchial spirochetes which may be responsible for chronic bronchitis, with or without asthma. Most cases are missed by the usual methods of examining sputum. The simple darkfield element (Bausch and Lomb) replaces the uppermost hemisphere of the Abbe condensing system. The spiral organisms, if present, are easily seen and identified. On several occasions, this routine method revealed spirochetes when not suspected.

The sedimentation rate and Weltman reaction in allergy may be compared. Parson[258] did 3,000 sedimentation rates in one year in patients with various allergic and nonallergic conditions. The Landau-Adams apparatus was used and the results noted at end of one hour. When possible, tests were made on each patient throughout the year, with frequent tests in seasonal cases during their seasonal exacerbations Normal was 1 to 10 mm.; infections were well over 25. Results were as follows: allergic migraine (nine cases), all 2 to 8 mm. except two who had temporary rise because of infectious complications; bronchial asthma (forty-five cases) (uncomplicated), 3 to 10 mm.; allergic bronchitis (nine patients), seven normal at start, with the other two at 20 and 26 mm. which returned to normal when the complicating infection was gone. Other allergic conditions were studied, and Parsons states that examination of sedimentation rates is very helpful in differentiating allergic and nonallergic conditions, and has avoided unnecessary allergy diagnostic procedures, on the one hand, and explained some failures, on the other hand. A high rate calls for search for infection. The percentage of error is small (5 per cent). The procedure should be routine.

Dutton,[99] on the other hand, prefers the Weltman reaction as a diagnostic aid, and calls attention to Dees' paper (1941), which first told of the value of this test in allergic diseases.[84] The technique is simple, and Dutton says the test is even more dependable than the sedimentation test in indicating an infection. It is easily applicable for use in a small laboratory and deserves a wider use.

A rapid and accurate technique for counting blood eosinophilia is described by Discombe:[93] one part of blood is diluted with twenty parts of staining fluid (five volumes each of 1 per cent aqueous eosin Y and of acetone and ninety volumes distilled water). The pipette is shaken vigorously. A normal eosinophile count is 0 to 240 per cubic millimeter. A mild eosinophilia (400 to 500 cells) was found in most quiescent asthmatics.

The usefulness of the leukopenic index estimation as regards allergy to foods is by no means dead. Several allergists in this country continue to use the method, and their experience and care in technique yield good results. In Norway, Lindeberg-Luidnet[216] obtained better results in two food-sensitive asthmatics by this method than by any other, including tests with food extracts.

To determine whether an x-ray shadow of maxillary sinus opacity is due to chronic infection or allergic edema. 0.5 to 1.0 c.c. of 1:1000 epinephrine is injected subcutaneously. Frouchtman and Ferrando,[129] in eight cases of allergic sinusitis, showed that the epinephrine lessened opacity as demonstrated by x-ray; the opacity is due to edema of the sinus mucosa, and this edema is reversible. In chronic allergic sinusitis with fibrosis, epinephrine reduces the mucosal edema but cannot entirely clear up sinus opacity.

Vilhena[358] emphasizes the importance of examination in asthma of sputum, nasal smear, blood, and other laboratory procedures, including search for fungi, bacteria, worms, and a tuberculin reaction. Millman[242] also discusses the diagnosis and differential diagnosis of respiratory allergy.

### BRONCHOSCOPY IN DIAGNOSIS AND TREATMENT

Because of the growing importance of the bronchoscope in the differential diagnosis and treatment of asthmas, it was thought best to gather the literature on this subject in one section. A good bronchoscopist is an invaluable aid.

One of the finest of all papers is that by Lell[211] on "Bronchoscopy in Diagnosis of Allergic Pulmonary Disease." In 176 children examined bronchocopically because of "asthma," 130 really had bronchial asthma. The others were: eighteen with

foreign bodies in the respiratory tract, five with foreign bodies in the esophagus, fourteen with tracheal compression, one with retropharyngeal abscess, and eight with organic changes in the larynx itself.

In 102 patients with status asthmaticus, 269 bronchoscopic examinations were made, and the pathologic findings were uniformly consistent: hemorrhagic and redundant mucosas greatly lessened the size of the lumina of the trachea and bronchi; thick tenacious secretion was always present; and, on expiration, collapse of the posterior wall of the trachea was always seen. These changes were confirmed in gross and microscopic studies in five patients who died in status asthmaticus. [Readers are urged to study this article.]

Holinger and Rigby[168] also have a fine article, with presentation of three cases. One patient had complete bronchus obstruction by a screw with resultant atelectasis and bronchiectasis. The second had mediastinal, pericardial and subcutaneous emphysema from a check-valve obstruction of a bronchus by a peanut. In the third case, a metallic foreign body partially obstructed a bronchus with no signs except localized wheezing.

They also point out that increased negative pressure on inspiration harms for the following reasons: (1) It leads to an increase in pulmonary capillary blood pressure with transudation of serum into alveolar spaces. This is a direct result of the increased negative pressure on the heart and circulation, which increases the return flow of blood to the heart so that blood flow through the chest is increased, with more blood in the left ventricle. As the negative pressure rises, these two effects increase until there is a progressive accumulation of blood in the lungs; this causes a rise in capillary blood pressure with resultant congestion, transudation and pulmonary edema. (2) Exudation of fluid into the alveolar spaces and bronchioles occurs because of the suction action of the intrabronchial and intra-alveolar negative pressure. (3) A vicious circle ensues; there is a further increase in negative pressure due to the attempt to compensate for the effects of the other two actions by increasing the respiratory effort.

Blake[33] points out the usefulness, in fact the necessity, in many cases of bronchoscopy in the diagnosis of the lesions which may involve the tracheo-bronchial tree, e.g., pulmonary tuberculosis, adenoma, carcinoma, foreign body, postpneumonic atelectasis or abscess. Unilateral bronchiectasis may heal after opening of an obstructed bronchus, and bilateral bronchiectasis may be improved by periodic bronchoscopic aspiration. Contrary to popular opinion, foreign bodies are the reason for less than 5 per cent of all bronchoscopic examinations. Kernan[196] also emphasizes the usefulness of the bronchoscope; aspirated secretions can be studied and can be used for autogenous vaccine therapy; the procedure is invaluable in differential diagnosis from bronchial asthma.

Rimér,[287] from Norway, aspirated material from the bronchi of twenty-six patients and instilled penicillin and/or sulfathiazole. These patients had such conditions as chronic, often purulent bronchitis, bronchiectasis, bronchostenosis and/or atelectasis. In all, the bronchial mucosa was congested and edematous, with sticky, gelatinous and tenacious secretion. Rimér says that the bronchial musculature was *spastic*. [This is not the finding my most bronchoscopists.] The cronchial secretion was sterile in only four of these twenty-six patients.

Hansen and Smidt[154] point out the value of bronchoscopic aspiration in preventing death in severe status asthmaticus—this by diminishing the tension of bronchial muscles and by removal of thick tenacious obstructing secretion. Deller,[87] from London, emphasizes the infectious etiology of bronchial asthma almost to the exclusion of allergy. He also finds bronchospasm forming a transverse slit at the bifurcation of the small tubes with resultant wheezing and dyspnea. Much tenacious sputum is seen, and the mucosa is swollen. He instills penicillin into the antra and has patients inhale penicillin. These procedures plus aspiration lead to "temporary cures" in 78 per cent. [Deller's statement that he saw bronchospasm without doubt in over 100 attacks of bronchial asthma certainly needs verification; we also deplore his use of morphine in the treatment of bronchial asthma.]

### DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

Glaser's article[141] on differential diagnosis of bronchial asthma in infancy and childhood is excellent. Unger's definition is not complete, says Glaser, who suggests that "Bronchial asthma may be defined as a form of obstructive emphysema of allergic origin, involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, chiefly expiratory, accompanied by wheezing heard on auscultation of the chest and typically relieved, at least in the early stages of an attack, by sympathomimetic drugs. The pathological physiology consists of edema, increased secre-

tion of the mucous glands, spasm of smooth muscle, and usually a local tissue and fluid eosinophilia." This definition emphasizes that bronchial asthma is only one form of obstructive emphysema, though the most common form. All "nonallergic asthmas" are other forms of obstructive emphysema and should be so designated. [We must remark that the above definition is not entirely correct because (a) mild attacks of true bronchial asthma are hardly emphysematous; (b) true asthma is not necessarily paroxysmal; many are chronic from onset; and (c) "cardiac asthma" is one form of asthma certainly not associated with emphysema.]

Glaser sees about four to six cases of bronchial asthma each year in infants under one, but most develop at four to five. The classical sequence is: colic, usually at three weeks; atopic dermatitis a few weeks later; recurrent upper respiratory infections at two to three, followed by hay fever or allergic rhinitis, then asthma. This progression is typical but not invariable. Asthma in children, especially at two or less, differs from adult asthma in four respects: (1) dyspnea is not necessarily expiratory; (2) orthopnea may not be present; the infant can often lie comfortably even on his back; (3) infants rarely show anxiety; and (4) fever is common, though rarely more than 1.5° F.

He uses epinephrine in small doses: under one, 0.10 c.c. to begin with, followed by 0.15 c.c. in fifteen to twenty minutes, if necessary; this is repeated if asthma is still present. He occasionally uses small doses of morphine, though he prefers demerol or dilaudid. [We object to opiates].

Bronchial asthma, says Glaser, must be differentiated from many conditions: (1) Asthmatic bronchitis is characterized by coryza, fever, poor response to ephedrine or epinephrine, preponderance of neutrophiles in nasal smears, and increased sedimentation rate. It may not be followed by bronchial asthma. (2) Foreign bodies in a bronchus are not uncommon; x-ray and bronchoscopy are mandatory if any possibility. (3) Cystic fibrosis of pancreas (case report with autopsy findings) has as chief symptoms the absence of good response to epinephrine and ephedrine, and of eosinophilia; failure to absorb glucose properly as shown by glucose tolerance curve; poor absorption of vitamin A as indicated by vitamin A tolerance test; diminution or absence of pancreatic enzymes on duodenal drainage. (4) Thymic asthma is rare, but may be helped by roentgen therapy. (5) Ayerza's disease is also rare (case report); chief symptoms are dyspnea, polycythemia, chronic cyanosis, prominent pulmonary conus with hypertrophy right ventricle, and right ventricular preponderance on electrocardiogram. (6) Dust bronchitis, previously noted in Dust Bowl, is due to inhalation of finely pulverized dust; cough is explosive, intractable, and non-productive, and fever and wheezing may be associated, with soft patchy mottling on x-ray. (7) Sighing dyspnea is a functional disorder. (8) Cough of whooping cough is characterized by no response to ephedrine or epinephrine, absence of eosinophilia, leukocytosis with relative lymphocytosis, positive culture for H. pertussis, no wheezing on forced expiration, and typical "whoop" which usually comes in three weeks. (9) Bronchotetany is rare, but dyspnea and wheezing may occur. Calcium intravenously gives brilliant results. (10) Cardiac asthma does not occur in infancy and childhood (White's youngest patient was eighteen, though Clausen reported cases at ages of eleven and twelve).

Chobot[66] has another paper on asthma in children. He does not like the term "asthmatic bronchitis." In his differential diagnosis he includes foreign bodies, whooping cough, transient pneumonias, bronchitis, lung tumors, tuberculosis, Loeffler's syndrome, and cardiac asthma.

Other articles deal with conditions which can simulate bronchial asthma. Frank's patient,[122] aged sixty-two, had a laryngeal carcinoma, but this did not initiate "asthmatic" attacks until roentgen treatment led to severe arytenoid edema with resultant partial obstruction of the larynx. Tracheotomy was necessary, and this relieved the obstruction, with cessation of "asthmatic" attacks. Holley[169] studied thirty-nine cases of bronchial adenomas. The predominent symptoms are cough, hemoptysis, expectoration, and recurrent acute respiratory infections. Lobectomy or pneumonectomy, depending on the location of the tumor, is the preferred treatment.

Bronchogenic carcinoma, says Van Ordstrand,[359] is now the third most frequent type of primary neoplasm, especially in males fifty to sixty years old. Seventy per cent originate in the central third of the involved lung, at or near the hilum in the main stem bronchus or its maior bifurcations; therefore, visualization is possible in about sixty-five per cent of the cases, and early bronchoscopy is essential. Cough with or without hemoptysis is an early symptom, frequently followed by partial or complete bronchial occlusion with possible atelectasis, pneumonitis or lung abscess. In the average patient symptoms were present for seven months prior to correct diagnosis. Van Ordstrand urges bronchoscopy and x-ray in any patient who

has an unexplained cough for more than six weeks. He also urges exploratory thoracotomy if there is a unilateral wheeze, yet x-ray and bronchoscopy are negative.

Isaacson and Rapoport [180] note the occurrence of eosinophilia in carcinoma, an abnormally large number of eosinophilic cells in the blood stream may indicate metastases. Disseminated growths were found in twenty-seven of thirty-four cases of eosinophilia with carcinoma. [We have recently had a forty-one-year-old patient, referred for asthma, who had inspiratory instead of expiratory dyspnea. Despite the finding of 2, 80, and 100 per cent sputum eosinophilia, laryngoscopy and biopsy revealed squamous-celled carcinoma at the carina, with almost complete obstruction of both primary bronchi.]

Progressive bilateral bullous emphysema was observed in eight men during a three-year period by Price and Teplick.[265] The process begins in the apices and gradually increases in extreme cases until both upper and lower lobes are replaced by large cyst-like areas. Cough, slowly increasing dyspnea, recurrent respiratory infections, cachexia, and asthmatoid attacks are the main symptoms, with death when insufficient pulmonary tissue remains, or from intercurrent infections. The etiology is unknown, but this condition may be similar to giant bullous emphysema, cystic disease of the lung, multiple cysts of the lung, cystic degeneration of the lungs, and vanishing lungs; these names have been given in cases previously reported. In all of these patients, similar features and x-ray findings are found, and in nearly all, the pulmonary conus of the heart becomes enlarged, with right heart strain. There is no effective treatment. Klosk and his co-workers[199] also write on "Cystic Disease of the Lung," with a report of twelve cases. Hemorrhage, infection, and spontaneous hemopneumothorax or pneumothorax occurred in the nine congenital cases. In three cases the condition was acquired and was associated with chronic bronchitis, peribronchitis, pulmonary fibrosis and "bronchial asthma." [In the three acquired cases associated with asthmatic symptoms, we believe that this is not a true cystic disease, but is merely bronchial asthma complicated by extensive formation of emphysematous bullae, a not infrequent finding; rupture may occur].

Alemany Vall, from Barcelona,[11] points out that pulmonary tuberculosis can cause an "asthmatoid" condition, and in some cases the similarity is striking.

Industrial dusts may cause lung changes. Wegelius[368] found 126 cases of asbestosis among 476 workers of the Finska Mineral Co. By x-ray, the condition was mild in ninety-four, moderate in twenty-three, and advanced in nine. The rather high percentage of advanced cases, as compared with statistics from other countries, is probably due to the recent recognition of this disease in Finland. Cardiac enlargement was less frequent than noted in other reports. Greenberg[149] found advanced fibrosis in thirty-two male workers in a group of tremolite talc miners and millers in northern New York State. All had worked with this talc for at least ten years; and in this group of 107 exposed that long, the incidence of fibrosis was 29.9 per cent. The fibrosis was of a fine diffuse type with the x-ray appearance of granulation or nodulation on a hazy background. Disability, with dyspnea, cough, and fatigue, was prominent, along with increased susceptibility to tuberculosis. In addition to fibrosis, "talc placques" were observed in the lungs of 6.3 per cent of all those exposed. Tremolite talc, says Greenberg, is a silicate dust capable, like asbestos, of causing a disabling pneumoconiosis.

In a similar study of 344 workers, inhalation of particles of alumina abrasives (bauxite) caused symptoms, says Shaver and Riddell.[314] Radiologic evidences of disease were found in thirty-five, with thirteen others classified as doubtful; fatality had occurred in seven. In several, the condition has progressed rapidly, with severe disability. The acceleration demanded by the war apparently was a major factor in increasing exposure, and cases observed in Germany seem to have occurred under similar circumstances of increased production. The disease is essentially an interstitial lung fibrosis, non-nodular in type, but may be associated with severe emphysema, with blebs and rupture with spontaneous pneumothorax. The process involves inhalation of alumina and silica, both in a very fine state of division, and of small quantities of many other substances.

*Cor pulmonale* very possibly results from similar pulmonary conditions, not all of them fibrosis, however. It certainly occurs very rarely in an uncomplicated bronchial asthma, no matter what the duration, even in those chronic asthmatics in whom emphysema is fairly severe. Spain and Handler[323] have an excellent paper on this subject, based on a series of sixty consecutive cases studied at necropsy. Those cases were selected in which there was no significant evidence of hypertension, valvular heart disease, congenital lesion, syphilitic cardiovascular disease, or coronary atherosclerosis, but with hypertrophy of the right ventricle. Underlying pulmonary conditions were emphysema in forty cases, bronchiectasis in six, bronchial

asthma in six, silicotuberculosis in three, pulmonary tuberculosis in two and one case each of kyphoscoliosis, pulmonary arteriolarsclerosis, and organized pulmonary thrombi. The authors discuss the role and methods by which each of these conditions can produce cor pulmonale. Errors in diagnosis are common: in about fifty per cent, arteriosclerotic heart disease is diagnosed. The main diagnostic findings in cor pulmonale are increase in size of the heart to the right, prominence in epigastric pulsation, accentuation of pulmonic second sounds, fluoroscopic and x-ray findings, and right axis deviation in the electrocardiogram.

From Madrid, Bozal Urzay and Diaz Opacio[41] reviewed sixty-nine cases of chronic cor pulmonale and two of acute. The acute cases, both fatal, came after abdominal surgery. Occupational exposures were important causes in thirty-five of the sixty-nine chronic cases (jute and blanket workers, miners, millers). Cough, dyspnea, cyanosis, and low blood pressure were frequent. Electrocardiograms revealed bradycardia, low voltage, ventricular complex of small amplitude and right predominance. Roentgen studies showed enlarged hearts, especially of the right side. Treatment is removal from dusty occupations, change of climate, and guarding against infections. In patients without decompensation the respiratory symptoms usually disappear following improvement of the circulatory system (rest, digitalis, mercurial diuretics, et cetera).

There are several articles on the differential diagnosis of asthma from heart disease. Oliveira Lima[253] advises determination of venous pressure, circulation time, radiography, et cetera. "Cardiac asthma" shows evidence of left ventricular strain or failure, e.g., hypertension with aortic valve defect, with prolonged circulation time, and associated diminution in minute volume and accumulation of metabolic products by anoxemia and embarrassment of respiratory center. Rutledge[299] speaks of cardiac dyspnea and the methods for determining its existence. He stresses differential diagnosis between cardiac and bronchial asthma. From Ukrainia, Mikhnev[237] states that World War II afforded an excellent opportunity for studying cardiac asthma. The pathogenesis includes increased venous pressure, decreased vital capacity and velocity of circulation, and increased mass of blood in the pulmonary circulation with a corresponding decrease in the minute volume of blood. There is arterial and venous anoxemia.

Plotz,[263] in a discussion of the mechanism of wheezing sometimes found in heart disease, concludes: (a) bronchospasm is an important element in certain types of heart disease; (b) cardiac asthma may occur with asthmatic wheezing and without basal râles; such cases are indistinguishable by physical signs from allergic bronchial asthma and may, like true asthma, be benefited by epinephrine; (c) epinephrine does not increase vital capacity in normal individuals; (d) epinephrine leads to sharp increase of vital capacity in patients with cardiac failure who wheeze but do *not* have basal râles, but (e) there is no effect in patients with basal râles; (f) expiratory pressure is sharply decreased in pulmonary congestion or wheezing conditions, and the expiration time is prolonged.

Berconsky and Neuman[27] studied fifty-one cases with mitral stenosis or mitral disease with paroxysmal dyspnea; auricular fibrillation was associated in some. Sudden pulmonary stasis in such cases appears to be due to (1) shortening of diastolic filling time of the ventricles and decrease in circulation to the ventricular muscle itself originated by tachycardia, and (2) greater relative obstruction of the mitral orifice caused by an increased venous return to the heart.

*Fungi* can cause pulmonary disease which may simulate bronchial asthma. It is important to search the sputum, as already pointed out by Dutton. Smith[319] has a fine forty-page article dealing with the various fungous infections of lung tissue. These include actinomycosis, blastomycosis, coccidiomycosis, cryptococcis (torulosis), moniliasis, geotrichosis, sportotrichosis, histoplasmosis, aspergillosis, penicillosis, mucormycosis, and infections of the lungs by *Bacteroides necrophorus, Actinobacillus* lignieresi, a peculiar form of staphylococcus, and spores of *Coniocorium corticale*, from exposure to the inner bark of maple logs.

Kunstadter and his associates[203] state that the symptomatic, radiologic and clinical findings of pulmonary geotrichosis are similar to those of other mycotic diseases. Such cases may simulate chronic bronchitis, bronchial asthma, pulmonary tuberculosis, and atypical pneumonia. Tuberculosis may coexist, but in any patient who apparently has pulmonary tuberculosis, with repeated negative sputa for tubercle bacilli, careful search should be made for fungi, and a therapeutic test with iodides will give good response in fungous cases. Sputum in such cases is typically white, mucoid with grayish flakes, and with a yeast-like odor.

Clark and Gilmore[68] injected a 1:100 coccidioidin extract into 372 individuals; positive reactions appeared in 125 cases, with negatives in all persons who had not

been in areas endemic for *C. immitis* infection. The positive skin test disappeared when two patients became very ill with the disseminated form of the disease. Complement fixation and precipitin antibodies for coccidioides may be found in blood, spinal and chest fluids in active stages of the disease. The skin test is similar to that with tuberculin.

A patient of Hiatt and Martin[164] had severe pulmonary moniliasis and failed to respond to the usual treatment (iodides and intravenous injections of gentian violet). Skin and agglutination tests were negative for *Candida albicans*. An intracutaneous test with *anti-Candida albicans* rabbit serum was strongly positive, with a negative control. Subcutaneous injections of this serum caused dramatic recovery, following which the agglutination test for the fungus was positive in 1:80 dilution. The skin test became slightly positive for a short time.

Rifkin and Eberhard[286] report a South Pacific island native whose clinical history, x-ray and laboratory findings suggested the diagnosis of pulmonary filariasis. Numerous microfilariae characteristic of *Wuchereria bancrofti* and many eosinophiles were found in the sputum and peripheral blood. Skin test with *Dirofilaria immitis* antigen was positive in 1:8,000 and 1:16,000 titres.

Histoplasmosis is discussed by Zwerling and Palmer.[381] The pulmonary calcifications found on x-ray in persons who live in the east-central part of the United States are more often associated with a positive reaction to histoplasmin than to tuberculin. This confirms previous work of Palmer who surveyed student nurses in eight large cities. The positive reaction to histoplasmin, therefore, probably indicates a previous infection which, contrary to earlier beliefs, is not necessarily fatal. Histoplasmosis is probably widespread, and the pulmonary calcifications which it produces closely resemble those of pulmonary tuberculosis. The incidence in negroes is even higher than in whites.

### THE TREATMENT OF BRONCHIAL ASTHMA

The *specific treatment* of bronchial asthma is discussed in all the new books and is mentioned in many of the general articles. But only two papers deal with specific treatment. This paucity continues to be an astounding fact, and probably indicates that the two pillars of this type of therapy, avoidance and hyposensitization, are now pretty well standardized. One must never forget that the highest percentages of clinical cure (relief from symptoms) and improvement occur in those fortunate patients in whom the cause can be found and eliminated or, at least, minimized by hyposensitization.

All other methods of treatment are symptomatic, and the large number of papers on these nonspecific measures, e.g., antihistaminic drugs and various methods of inhalation therapy, make us wonder whether we are not departing too much from that narrow and straight path of specific treatment. In our enthusiasm for newer drugs and newer techniques, we must not forget that if one can prevent exposure or minimize it, these new drugs and procedures will not be necessary. This does not mean that the recent progress along these lines is not helpful; it is of great aid in many allergic patients, but we must not forget the principles on which the whole success in the field of allergy is based, i.e., the search for and removal of the cause, where possible.

Goodman[146] stresses the necessity of removing the offending substance as thoroughly as possible. He has four essential rules in his program of desensitization: (1) the solution contains the major reacting allergens, i.e., he mixes pollens, dust, dander, molds and vaccines in one vial. [we always separate tree, grass, ragweed pollen extracts, and vaccines]; (2) he begins with a dilution which will not cause a local or systemic reaction; (3) the dosage is progressively increased until a fairly concentrated solution is given without reaction; and (4) the patient's tolerance is then maintained by injections at regular intervals. Causes for poor results include (a) stopping treatment too soon, (b) interruption of schedule of injections, (c) continuation of contact with allergens, (d) failure to discover all responsible factors, (e) active foci of infection, especially in upper respiratory tract, and (f) situational factors, e.g., asthma may be convenient for some persons and may serve a purpose which makes the patient reluctant to part with it.

Von Dishoeck and Klein[361] studied inhibiting antibodies. During hyposensitization with grass pollen extract, an increase in the reagin titer of serum occurred before the development of the inhibiting antibodies; these latter were also demonstrated in sera of patients treated with injections of extracts of tobacco, orris root, beans, and wheat, but never with house dust despite good clinical results in dust-sensitive patients. Although high dosage and high inhibiting antibody titer seemed to corre-

late with good clinical results, satisfactory relief was often obtained in complete absence of this antibody.

### ANTIHISTAMINIC DRUGS IN TREATMENT OF BRONCHIAL ASTHMA

There is a veritable flood of papers on the use of the so-called antihistaminic drugs in the various allergic diseases. Most of these new drugs relieve nasal congestion and pruritus, but have not been of particular help in bronchial asthma. We deal here with these drugs as applied to asthma; most of the reports are on Benadryl and Pyribenzamine, but reports on newer drugs are beginning to appear.

An interesting paper comes from Curry.[80] Histamine itself was injected intramuscularly and intravenously. There was no effect in ten normal persons nor in ten allergic patients, including asthmatics, who were free from asthma at the time. But in patients with varying degrees of chronic bronchitis, emphysema and asthma, histamine caused bronchoconstriction and lessened vital capacity in eight of nine cases. The degree of constriction was closely correlated with the dose of histamine, but varied somewhat with the patient and the severity of the asthma. During any single period of observation the same degree of constriction of the bronchi could be produced by identical amounts of histamine; the height of the reaction was thirty seconds by vein, two to three minutes by muscle. If given sublingually or by nebulization, there was definite but less pronounced constriction.

Loew and his associates,[219] in guinea pigs, produced bronchoconstriction by exposure to atomized histamine solutions. The counteracting drugs, in order of efficiency, were epinephrine, Benadryl, Demerol, atropine, papaverin, and aminophylline. Ephedrine, morphine, pentobarbital, Transentine, Pavatrine and Syntropan were ineffective.

*Benadryl* has received much attention. Levy and Seabury[215] studied the pulmonary volume, respiratory rate, minute ventilation, oxygen consumption, and ventilator equivalent of sixteen patients with "extrinsic" asthma, both before and thirty and sixty minutes after ingestion of 100 mg. of Benadryl. The drug caused no consistent change in any of the measurements, though six patients were clinically improved. Five patients who received 0.3 mg. epinephrine and 0.25 gm. aminophylline showed a uniform effect characterized by increased vital capacity, tidal air, minute ventilation, and expiration differential, with no increase in rate of respiration.

Bowen[39] was greatly disappointed, despite reports from Parke, Davis investigators, in which 63.5 per cent improvement was claimed in studies of 343 asthmatic cases. Benadryl helped less than 10 per cent of cases of bronchial asthma. Logan[220] reports improvement in six of seven children treated for single attacks of asthma, and in sixteen of seventeen children who had multiple attacks. He favors the combination of iodides and Benadryl in nonseasonal asthma, and his dosage varied from 10 to 450 mg. per day. Todd[344] obtained complete relief in four of eighteen patients with asthma, with partial relief in ten; and in six patients with asthma and rhinitis, he obtained complete relief in two and partial in three. Waldbott[364] found Benadryl unsuccessful in sixteen of thirty pollen asthmatics and in twenty-four of forty-eight cases of perennial asthma. One seven-month-old infant obtained excellent relief from severe asthma following 50 mg. Benadryl, but in three patients severe attacks of asthma followed the drug. Symptomatic relief occurred in eight of twenty cases of asthma, as reported by Schwartz and Levin.[306] S. J. Levin[213] gave 50 to 100 mg. every four to six hours, with maximum of 300 mg. several times daily, with 5 to 20 mg. dosage in children. He found Benadryl practically useless when a respiratory infection either caused the attack of asthma or complicated it. Improvement occurred in ten of fifteen asthmatic children, and in forty-seven of seventy-two asthmatic adults, with aggravation of asthma in four patients.

From the Mayo Clinic, improvement occurred in fourteen of nineteen patients who had both hay fever and asthma, but of these, five noted relief of the hay fever but not of the asthma, say Koelsche and his co-workers.[200] Benadryl helped four of twelve asthmatics. Jenkins and his Ann Arbor associates[186] also obtained indifferent results from Benadryl, given intravenously in eight patients. In twenty-three cases of asthma, thirteen of whom had associated allergies, only two of the six patients who obtained excellent results were having severe asthma. Goldstein[144] treated seventy-nine allergic patients with Benadryl; he obtained better results in other allergic conditions than with asthma. In 50 mg. doses, Benadryl relieved mild wheezing and dyspnea in five of sixteen of Eyermann's patients;[108] but relief was neither as prompt nor as effective as that from oral 0.03 gm. ephedrine. Severe asthma was not relieved by as much as 100 mg. Benadryl orally. Barnett[25] and his co-workers report poor results in three severe asthmatics. No response occurred in four of eight cases of bronchial asthma, say Blumenthal and Rosenberg;[36] Benadryl relieved symptoms in two cases of cardiac asthma. Cohen and his associates[70]

state: "One asthmatic patient in an acute attack was given 8 mg. intravenously in five minutes. The attack was controlled completely." A Friedlaender[125] reports no benefit in asthma, and S. Friedlaender and Feinberg[126] also found that Benadryl did not help sixteen chronic asthmatics, and Taub[339] confirms this.

Side reactions from Benadryl have been reported by each of the above workers, some more emphatically than others. In addition, Borman's[38] patient, an eighteen-year-old girl took forty capsules (2,000 mg., self-administered) during three days of hay fever and asthma. She became drowsy and irrational, but recovered in forty-eight hours. A three and one-half-year-old boy was given 100 mg. Benadryl for relief of hay fever; six hours later he received 100 mg. again; in twenty minutes the boy was laughing, singing, and irrational, and had involuntary twitching and urination and spastic movements, with recovery next day. [The dosages were obviously too high for these last two patients.] McGavack and his associates[232] also found that Benadryl is a potent sedative, with vertigo, blurred vision, and reduced blood pressure in some of their patients. The drug did help four asthmatics. Three of ten patients who were given 20 to 30 mg. intravenously developed chills, vertigo, headache, low back pain, nausea, drowsiness, and extreme pallor.

*Pyribenzamine* has also received much attention although it was put out for clinical studies a little later than Benadryl. Mayer and his associates[230] have done a great deal of work with this drug in animals. There is a large margin of safety. In man, doses up to 500 mg. per day are usually well tolerated, and the antihistaminic properties of the drug are well proven by its action on intestines, uterus and bronchial muscles of the guinea pig.

Arbesman and his associates,[17] in a study of 495 allergic patients, state that Pyribenzamine relieved or prevented dyspnea and cough in 48 per cent of ninety-eight asthmatics. Side effects occurred but were not serious. The average daily dose was 100 to 400 mg., by mouth. One interesting point: the drug can prevent the onset of asthma from exposure to an allergen, e.g., cat, dog or horse dander, and coffee dust. [This prompts the thought that about 100 mg. doses every four hours might prevent attacks of asthma in those in whom "colds" usually result in asthma.] Friedlaender and Friedlaender[127] report that only two of thirty nonseasonal asthmatics were benefited by this drug, although it was of aid in sixty-nine of 108 cases of allergic rhinitis and in various types of pruritus and hay fever. Feinberg and Friedlaender[110] likewise found the drug has only moderate effectiveness in bronchial asthma.

A committee of the American Academy of Allergy[271] collected statistics from thirteen men, including Arbesman, from various parts of the United States. In a series of 529 cases of bronchial asthma, seasonal and nonseasonal, Pyribenzamine helped 135 (26 per cent). Peculiarly enough, no improvement resulted in 100 cases reported from Florida, and only 17 per cent and 8 per cent in ninety and 209 cases from the New York area and the Midwest, respectively, were improved. There obviously is a great difference of opinion among workers as to what constitutes "improvement."

*Antistine,* another of this group, was given in doses of 100 mg. six times a day by mouth and/or 100 mg. intravenously or intramuscularly. No unfavorable side effects are reported by Kallós, but there was no benefit in twenty-three cases of bronchial asthma.[192] Schindler[302] found only some improvement in six of ten cases of bronchial asthma, using Antistine in patients at the University of Basel. The drug was given orally, intramuscularly and/or intravenously.

*Antergan,* another one, was used by Schwartz and his associates in Norway.[305] The drug failed to help nineteen cases of hay fever, eleven of allergy to flour in bakers, and three cases of aspirin allergy. Side effects were frequent. Frouchtman[130] gave oral Antergan in daily doses of 0.40 to 0.60 gm. for three to six days, with improvement in two cases each of urticaria and allergic rhinitis, but no benefit in two cases of asthma. Undesirable side effects were common.

In addition to the above papers on individual antihistamine drugs, some authors compare the efficiency of one with the others. Curry[81] produced bronchoconstriction, with lessened vital capacity, by injecting histamine in certain asthmatic patients. Intravenous injections of 10 to 30 mg. of Benadryl gave excellent protection against this constriction; Pyribenzamine was tried orally in 50 mg. doses and gave little protection (not tried intravenously). Atropine was fair, but aminophylline, ephedrine and epinephrine were excellent in this respect. Rose and his co-workers,[292] in a study of the effects of Benadryl, Pyribenzamine, Antergan and Neoantergan, conclude: (a) the protection against anaphylactic shock by these four drugs decreases as the amount of the drug is decreased; (b) protection from the four drugs was very similar; (c) findings on the sensitized intestinal strip of the guinea pig bear out the

lack of difference in protection rendered by Benadryl and Neoantergan in anaphylaxis in the intact animal; (d) against a single lethal dose of histamine these drugs are almost equally effective; (e) observations on the sensitized intestinal strip indicate that the anaphylactic contraction was inhibited by an amount of antihistaminic drug which had no effect on the contraction of the same magnitude due to histamine.

They also state that in a series of patients with asthma, inhalation of these drugs has given much more encouraging results than when the drugs are given by mouth.

Feinberg[111] has a long article summarizing the literature on histamine, Benadryl and Pyribenzamine as they affect various allergic conditions. As regards asthma, in his own experience, Benadryl gave definite relief in only 12 per cent of fifty patients, chiefly perennial. Better results followed Pyribenzamine, with improvement in thirty-four (28 per cent of 121 patients; the relief, however, was only moderate, and not nearly as good as that from epinephrine. Moreover, this drug did not prevent the asthma which frequently accompanies hay fever.

Ratner,[278] whose views are shared by others, concludes that the release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions; hence any therapy based on such a concept must be called into question. The so-called antihistaminic drugs have not proved valuable in eradicating allergic conditions. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction. Benadryl and Pyribenzamine do alleviate symptoms in diverse allergic conditions and should have a place along with epinephrine, ephedrine and atropine as excellent antispasmodics. They are not very efficient in asthma and eczema, and they are not cures, some of the public and some physicians notwithstanding. Mayer[231] likewise is not convinced. The mechanism of these drugs is still in doubt, but they do have antihistaminic qualities. Since this is so, further study should unearth the pathogenic role of histamine in numerous manifestations in which such a role has never been suspected or throw overboard other cases of so-called allergy in the origin of which histamine has been falsely accused.

[From this survey of the literature on these drugs one can see that they are only slightly effective in asthma when given by mouth. Perhaps intravenous or aerosol methods may give improved results. The role of histamine or H-substance in clinical allergy still remains in doubt.]

*Histamine-azoprotein (Hapamine)* continues to draw a little undeserved attention. Dundy and his co-workers[97] tried it in twenty allergic children, of whom nine had asthma, and in twenty allergic adults, of whom three had infectious asthma. The drug was generally ineffective, both in asthma and in other allergic conditions, and severe local and some general reactions occurred in ten per cent. The authors agree that the histamine theory of allergy has *not* been proved. M. B. Cohen and Friedman, [71] almost alone, still maintain that the drug is of value in urticaria and in certain cases of bronchial asthma. Systemic reactions, they state, rarely occur, but "large local reactions are to be expected and are harmless." In a series of nineteen asthmatics, injections of this drug led to excellent results in eight, improvement in one, and failure in ten [but the authors state that the cases were under observation from four to twelve months, chiefly less than one year, and we all know that any new treatment, even water, can bring temporary relief in certain impressionable asthmatic patients. Furthermore, in seventeen of their nineteen asthmatics they report "etiology unknown." This high percentage may mean that these seventeen are non-reactors, perhaps even "bacterial" asthmatics, but we suggest that complete scratch and intradermal tests should be tried again.]

### ANTIBIOTICS IN TREATMENT OF ASTHMA AND RELATED CONDITIONS

Our statement in the review of the 1945 literature[349] still holds good: "It is therefore difficult at this stage to decide the position of penicillin in the treatment of bronchial asthma. It frequently cures or lessens infectious complications of asthma. Good results seem obtainable both by the usual intermittent injections of penicillin and by the newly developed aerosol technique. But chronic asthma, I am afraid, will still remain after the infection has been removed." Neither the writings of others nor our own added experience in the use of antibiotics changes this opinion.

Penicillin by intermittent injections is widely used in treating the infectious complications of asthma and in other infectious respiratory conditions, e.g., bronchiectasis. The use of sulfonamides in hospital practice seems to have lessened because of possible dangerous reactions, and streptomycin reports are still meager in chest conditions except for its promising results in pulmonary tuberculosis.

Leopold[212] studied eighty-five patients admitted to army hospitals in 1944 and 1945. Infectious or intrinsic chronic perennial asthma was present in sixty-two,

and "extrinsic" asthma with superimposed acute bronchitis or bronchiolitis in the other twenty-three. When the usual allergy treatment failed, penicillin was injected (40,000 units every four hours, with a minimum of 1,680,000 and a maximum of 10,800,000 units in a period of seven to thirty-one days). Results were not encouraging; the symptoms and signs of chronic perennial asthma of the infectious type were not cleared permanently; temporary and partial improvement occurred in twenty (32 per cent). The signs of asthma were not completely cured in any case, and seventy-six (89 per cent) of the total of eighty-five cases were not improved. The volume of sputum was decreased and remained so after treatment in twenty-one (33 per cent of the infectious group; and six (26 per cent) of the patients with superimposed bronchitis also had less sputum. There was practically no change in organisms cultured from the sputum of sixty-nine patients (81 per cent).

Miller[240] gave penicillin intramuscularly to twenty-nine "intrinsic" asthmatics. It is not a panacea for this type of asthma, but it is effective in a small but worthwhile proportion of infectious cases. All cases were in the hospital, and the control of any intrinsic factors was maintained. The dosage was 12,500 to 25,000 units every three hours, with an average total dose of 1,300,000. Excellent response occurred in eleven of the twenty-nine patients, improvement in eleven, no relief in seven. Relapse occurred in four of the "excellent" group, and in six of the "improved," when penicillin was stopped.

Kaufman's patient[193] had severe infectious bronchial asthma, and was relieved by injections of 10,000 units penicillin every two hours, with a total of 1,900,000. Wheezing did not return for two months. Bauman and his associates[26] treated twelve adults and twenty-four children ("bacterial" asthmas) with three penicillin tablets (20,000 units each) orally, every three hours for three days, day and night, with a total of 1,440,000 units. Blood levels were satisfactory (0.03) in all but three cases. Pneumococci were eliminated from nasal cultures, but staphylococci were not much affected. Clinical results were good for six weeks to four months in 71 per cent of thirty-six cases.

Boyd and Dorrance[43] found that some of the sulfa drugs, especially sulfadiazene, have an expectorant action, with an increased rate of output in the bronchial secretion. They worked with animals but suggest that sputum in man will also contain the drug, if administered.

*Inhalation penicillin therapy* has become very popular. As an editorial in ANNALS OF ALLERGY states,[100] priority in this field belongs to Abramson; he worked with aerosol penicillin and with other aerosol projects while with the Chemical Warfare Service, and was awarded the Legion of Merit. In an excellent paper,[2] Abramson discusses the principles and practice of aerosol therapy of the lungs and bronchi. He tells how the work was initiated; gives definitions of aerosol, atomization, nebulization, vaporization, and aerosolization; describes in detail large particle atomization and small particle nebulization; states that rebreathing is inefficient; describes simple apparatus and discusses its use with epinephrine, penicillin, streptomycin, sulfonamides, and hydrogen peroxide. For nebulization he prefers the De Vilbiss 40 or the Vaponefrin. He adds 25 per cent glycerol to 1:100 epinephrine to stabilize the solution.

Hydrogen peroxide solution, with 10 per cent glycerol in physiologic saline, is readily nebulized without loss of stability, whether used as hydrogen peroxide directly or as urea peroxide. There is no appreciable irritation. This aerosol was used in cases of asthma, asthma with infectious bronchitis, bronchiectasis and lung abscess, and was alternated with penicillin aerosol. Both Gram-positive and Gram-negative organisms can be destroyed by this combination.

Barach and his associates[22] have also been active in inhalation therapy. In the treatment of severe asthma, they discuss inhalation of oxygen and helium and Demerol by injection. They advise inhalation with penicillin in moderate dosage for one to three months. Inhalation of sodium sulfathiazole (1 to 5 per cent) is helpful in bronchopulmonary infection, but the authors prefer penicillin because of its greater bacteriostatic power against streptococci and staphylococci, and the fact that its bacteriostatic action is not inhibited by purulent secretions or P-aminobenzoic acid. They use 50,000 units penicillin in 1 c.c. of normal saline, with inhalations every three hours; this gives satisfactory blood levels. [Abramson points out that inhalation therapy helps by its direct action on the respiratory tract; he is not too much concerned about blood levels.]

In a series of eighty-six courses of treatment in fifty-one patients with chronic hypertrophic pulmonary emphysema Barach, et al, felt that improvement due to penicillin aerosol was marked in twenty, moderate in nineteen, slight in twenty-five, and absent in twenty-two. Other methods of treatment (physiologic therapy) gave

markedly good results in nine, moderate in thirty-six, slight in twenty-three, and none in eighteen. Of the sixty-six improved cases, thirty-one seemed more influenced by physiologic therapy, twenty-seven by penicillin, and eight by both equally.

Segal and his associates[307] helped many patients, some dramatically, by giving penicillin aerosol to eighty-five patients with bacterial pneumonia, suppurative bronchitis, bronchiectasis, lung abscess, infective bronchial asthma, infective laryngotracheobronchial edema, and emphysema. Generally, 25,000 units of penicillin were dissolved in normal saline and inhaled at three-hour intervals. A nebulizer was used which gave a fine mist. Streptomycin can be combined with penicillin in an aerosol. In a later report, their results in twenty-two cases of infective bronchial asthma were disappointing, although striking improvement was occasionally observed. Their results in bronchopulmonary infectious conditions continued to be good. Reactions were few (bronchospam, two instances of urticaria, and four of stomatitis in 118 patients). Segal also has a long article on "Progress in Inhalation Therapy," in which he reviews the literature. Strangely enough, he does not mention Abramson's studies which preceded those of Bryson and others.

Prigal and his co-workers[266] favor the use of a combined steam generator and aerosolizer. They also use other methods, e.g., the tent, which is best for infants and children. The steam generator can be used in the office or at home. It is inexpensive and safe, and any aerosol can be used.

Finke, in seventy-two patients with respiratory disease,[112] found no benefit from penicillin aerosol in two cases of intrinsic asthma; in ten patients with "mixed allergic-infectious" asthma the response was good by combined aerosol and control of allergic manifestations. Fishman[116] obtained good results in fifteen cases of infectious complications of asthma by using an ordinary nose and throat atomizer and 100,000 units of sodium penicillin solution in 50 c.c. of distilled water. 1 c.c. of this solution (pH 6) is inhaled as one dose every three hours. This is confirmed by Morse.[247] Hamburger and his associates,[153] by measurements of voluntary apnea and the speed of expired air, conclude that the "treatment of asthma by aerosols gives results superior to the various other types of treatment of this affection." [We must dissent from this view.] Toch and Steele[343] obtained good results in three elderly asthmatic patients who also had infectious processes in the lungs, and in one asthmatic who also had auricular fibrillation and congestive heart failure. They point out that penicillin, by whatever route, cannot be expected to cure "long-standing chronic bronchitis or chronic bronchiectasis, or asthmatic bronchitis with emphysema and fibrosis of the lungs or chronic sinusitis accompanied by polyposis and thickened lining membrane."

Southwell,[321] in a study of forty-three patients with bronchiectasis, bronchitis, or asthma, gave penicillin inhalations on an out-patient basis; a course of treatment consisted of 1,000,000 units given in inhalations of 100,000 units two to three times daily. In seventeen cases of chronic bronchitic asthma, one cleared entirely and all but three were improved, but there was no improvement in four cases of allergic asthma. Englesher[105] used 20,000 units every three to four hours for two to four weeks in seventy-four chronic asthmatics; only 15 per cent were slightly benefited, and 85 per cent received no benefit. In many of these patients parenteral penicillin was also used, also without results. Seltzer[310] likes the DeVilbiss 40 nebulizer, and when it becomes obstructed he washes it through a small hypodermic needle attached to an ordinary syringe.

Many other papers discuss aerosol penicillin, especially as used in the treatment of bronchopulmonary infection. In bronchiectasis not suitable for lobectomy, Siltzbach[316] was able to lessen the volume of sputum in ten of thirteen cases, along with a lessening of infection and the odor of the sputum. Bobrowitz and his co-workers[37] treated sixteen patients with severe bronchiectasis with a total dosage of 550,000 to more than 5,500,000 units over four to 115 days. Best results were obtained when the penicillin was instilled in the trachea; less effective was inhalation; least effective injections. Results were excellent during administration, i.e., reduction in amount, odor and pus in sputum, and elimination of most bacteria, and marked symptomatic relief. Treatment must be continued indefinitely as relapse occurs on discontinuance.

Fullerton and Shane[132] used penicillin aerosol in fourteen patients with bronchopulmonary disease. Virus pneumonia was not aided, but good response occurred in four cases of lobar pneumonia and in lung abscess. There was no alleviation of the asthmatic state in five patients. In nine cases of chronic bronchiectasis in which penicillin aerosol failed, Olsen[255] tried streptomycin; this removed Gram-negative bacteria and lessened the volume of sputum. Olsen advises combined penicillin and streptomycin aerosol preoperatively for pulmonary resection and as a temporary

measure in non-surgical bronchiectasis. Hanks[152] used small amounts of penicillin in aerosol, but obtained good results in thirty-four patients with respiratory infections, including virus pneumonia. Pyle[270] was able to eliminate penicillin-sensitive bacteria from the sputum of three patients with bronchial asthma and bronchiectasis, but the aerosol did not change the underlying pathologic condition.

Humphrey and Joules[173] studied various pulmonary diseases. Penicillin by inhalation gave excellent results in acute and subacute infections, but results with chronic infections were much less evident; of the eighty cases, forty-six were much improved, seventeen improved, and seventeen not improved. Levine[214] studied forty-two patients with chronic bronchiectasis in whom all previous treatment had failed, including parenteral penicillin. Penicillin aerosol was given every three hours for three to four weeks in doses of 1,000 to 20,000 units per c.c. Complete relief of symptoms occurred in nineteen, improvement in fourteen, and no relief in eight, but Levine, as do all others, points out that symptoms and bacteria return when the aerosol is stopped. In four asthmatic patients Hurst[175] obtained improvement by aerosol in two, one of whom developed angioneurotic edema on the ninth day.

Pulmonary instillation of a mixture of penicillin and iodized oil has been tried in bronchiectasis and lung abscess. Results are still uncertain.[101]

Thus we see that the above writers are fairly well agreed that inhalation of penicillin is excellent in treating bronchopulmonary diseases, especially if acute. It is less effective and gives only temporary benefit in bronchiectasis; it is useful in the infectious complications of asthma, but of little or no benefit to the underlying asthma. Our own experience in our asthma rooms at Wesley Memorial Hospital, Chicago, in a large series of cases, confirms these findings. We have used penicillin (and streptomycin in a few cases) both by injection and by inhalation; sometimes we have used both at the same time. The underlying asthma persists in many cases, but we are pleased with the method because the fever, high sedimentation rate, and leukocytosis usually clear, and the patients feel better. Our results in bronchiectasis have been mediocre, except when lobectomy is possible.

*(To be concluded in March-April issue. Complete list of references will appear with final installment.)*

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## PHYSIOLOGY OF THE LUNGS AND THE ASTHMATIC STATE

*(Continued from Page 63)*

An attempt was made to produce congestion of the lung in the living animal and to determine its effect on the distensibility of the lung. This was accomplished by placing a rubber-tipped clamp on two or three of the pulmonary vein and their entrance to the left atrium. This clamp acted very much like a severe mitral stenosis with pulmonary congestion. The volume-pressure curves obtained with the pulmonary veins occluded showed a decrease in distensibility of the lung.

WANTED—Resident and Fellows in Allergy. Facilities for clinical work and research available. Period of training of one year or longer with compensation. GRAHAM-THOMAS CLINIC, 201 West Franklin Street, Richmond 20, Virginia.

# ✶ *In Memoriam* ✶

**PHILIPP SCHONWALD, M.D., F.A.C.A.**

Dr. Philipp Schonwald, physician who attained world acclaim for discovery of a Penicillin substitute, passed away at his home in Seattle, Washington, in December, 1947. Dr. Schonwald was born and educated in Vienna. His 43-year medical career began in 1904 with his graduation from the University of Vienna Medical School. A long-felt desire to come to the United States prompted him to leave a post as chief of the medical staff of a large sanitarium near Vienna. He went to Seattle in 1921 as an established chest specialist. He was a pioneer in thorocoplasty, pneumothorax and intrapleural pneumolysis having performed many of these operations for tuberculosis, in their early development. He realized that many non-tuberculosis chest diseases were of an allergic nature and this led to his pioneer studies in allergy and related fields which he carried on to his last day. Dr. Schonwald was one of the original investigators on the allergic factor of soil bacteria and an early investigator on allergies traceable to mold spores. A great deal of his latter work was carried on while he was a wheel chair invalid. Six years ago he suffered a stroke which caused a left hemiplegia. He continued to publish many articles on allergy, molds and fungi, and their clinical application. A paper describing his search for an antibiotic to attack bacteria in the human colon will be published soon. He was an active member and contributor to scientific allergy as well as tuberculosis organizations and journals.

During twenty-six years' practice in Seattle Dr. Schonwald served on the staffs of the Riverton, Morningside and Swedish hospitals. He was a member of the American Medical Association, King County and Washington State Medical Societies, the American Trudeau Society and the International Correspondence Society of Allergists. He was a Fellow of the American College of Chest Physicians, American Academy of Allergy, American College of Tuberculosis Physicians, American College of Physicians, the International Association of Allergists and the American College of Allergists.

The College deeply regrets the loss of such a loyal friend and the members extend their most sincere sympathies to the family.

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RESTRICTED DIET FOR DETERMINATION OF SUSPECTED FOOD ALLERGY. First Edition. St. Louis 2, Missouri: Ralston Purina Company, 1946.

This is a diet sheet compiled by Miss Elspeth Bennett, Manager, Nutrition Service, Ralston Purina Company, in collaboration with a panel of allergists. It is intended for use when the physician wishes to apply dietary means in the difficult task of tracking down offending foods. Though no one diet can be applicable to all such cases, this one, made up as it is of a carefully selected list of foods to which few persons are sensitive should find wide application. Detailed information clearly given simplifies the problem of such a restricted diet for both physician and patient.

Menu guides and tested recipes make possible a variety of appetizing meals despite the limited number of foods. Timely buying information is also given. This new diet should prove a valuable addition to the wheat-free, egg-free, milk-free and wheat-egg-milk-free diet sheets that the Ralston Purina Company has made available to physicians for many years. As with these other diets, this new one is available to physicians in pads of twenty-five diet sheets.

# News Items

## NEWS OF SOCIETIES

The Ohio Valley Allergy Society will hold its next meeting at Springfield, Ohio, May 22, 1948. Dr. Armand Cohen of Louisville, Kentucky is Chairman and Dr. D. J. Parsons of Springfield, Ohio, is the Secretary-Treasurer.

* * *

At the annual meeting of the Los Angeles Society of Allergy (a Section of the Los Angeles County Medical Association), the following officers were elected for 1948:

President—Willard S. Small, M.D., Pasadena

Vice President—Hyman Miller, M.D.

Secretary-Treasurer—Frank G. Crandall, Jr., M.D.

George Piness, M.D., who was the president during 1947, was elected to the Executive Council for 1948.

These officers were installed at the January meeting of the Society.

* * *

At the November meeting of the Pittsburgh Allergy Society, the following officers were elected and committees appointed:

President—Lester Bartlett, M.D.

Secretary-Treasurer—Mayer A. Green, M.D.

*Membership Committee*—A. R. McCormick, M.D., Chairman; J. Gordan, M.D., and W. Ruehl, M.D.

*Program Committee*—Sylvia Wechsler, M.D., Chairman; R. Hamilton, M.D., and A. H. Neidorff, M.D.

*Pollen Commission*—E. P. Claus, Ph.D., Chairman; J. Mansmann, M.D.; P. Blank, M.D., and L. Criep, M.D.

## CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The spring meeting of the Central Pennsylvania Allergy Society will be held in York, Pennsylvania, at the Yorkshire Hotel on April 1, 1948. The luncheon and business meeting will take place between 11:00 A.M. and 1:00 P.M., and the scientific session will follow. The banquet for members and their wives will be held in the evening, with Lt. Governor Strickler of Pennsylvania as the principal speaker. All members are urged to attend and other physicians interested are welcome.

### Program

1:25 Address of Welcome—CHARLES FACKLER, M.D., President of York County Medical Society.

1:30 "General Concepts of Allergy"—A. HARVEY SIMMONS, M.D.

1:45 "Treatment of Bronchial Asthma"—ETHAN ALLAN BROWN, M.D.

2:30 "The Place of Irradiation of the Nasopharynx in the Treatment of Selected Cases of Asthmatic Bronchitis in Children."—JOHN E. BORDLEY, M.D.

3:00 *Intermission*

3:15 "Cytology of Nasal Secretions with Special Reference to Allergic Diseases."—M. VALENTINE MILLER, M.D.

4:00 "Headache from the Allergic Point of View."—FRANK F. FURSTENBERG, M.D.

4:30 "Mycotic Infection of Bronchi and Lungs—Their Relationship to Allergy."—LEO H. COLLINS, M.D.

5:00 "Role of Anti-histaminics in Allergy."—MERLE MILLER, M.D.

## SUSTAINING MEMBERSHIP

In the September-October issue of the ANNALS OF ALLERGY, an announcement was made in these columns of the establishment of Sustaining Membership by the College. This has been the custom of a number of scientific organizations for some time, such as is done by the American Society of Bacteriologists. It is logical that these firms associated with the allergists, both in a business and a co-operative way, be recognized as Sustaining Members. All of these members will be listed in each issue of the ANNALS and will receive subscriptions to the ANNALS. We are very pleased to introduce in this issue the first list of Sustaining Members of the American College of Allergists (Page xii).

## TWENTIETH ANNIVERSARY YEAR OF HAROFE HAIVRI

The attention of the medical profession is directed to the appearance of the Fall issue of *Harofe Haivri* (The Hebrew Medical Journal), a semi-annual bilingual publication edited by Moses Einhorn, M.D.

In the medical section, the following subjects are offered: "The Importance of the Rh Factor in Clinical Medicine" by Philip Levine, M.D., and Pharmacology and Toxicology of Streptomycin" by Ernst Pick, M.D.

The section on Palestine and Health contains the following articles: "The Contribution of Bacteriologists for the Control of Infectious Diseases in Palestine" by L. Olitski, M.D., of the Hebrew University; "The Present Status of Tuberculosis in Palestine" by A. Wolowelsky, M.D., and "Plastic Surgery in Palestine" by Ernst Wodak, M.D.

Under the heading of Historical Medicine Dr. Leon Nemoy of Yale University writes on the great philosopher and physician of the 13th century—Ibn Kammuna. Dr. Yom-Tov Levinsky discusses in his article on Folklore Medicine, the legends surrounding frogs and spiders as healing agents.

The original articles are summarized in English to make them available to those who are unable to read Hebrew. The editorial office of *The Hebrew Medical Journal*, 983 Park Avenue, New York 28, N. Y., will be glad to furnish any further information desired.

## NATIONAL BLOOD PROGRAM

Mr. Louis C. Boochever, Director of Public Relations of the American National Red Cross, National Headquarters, Washington 13, D. C., announces:

"The American Red Cross is undertaking one of the most far-reaching peacetime projects in its history—a National Blood Program which promises to be a valuable adjunct to medical science in protecting the health of the American people. The Program will provide whole blood and its derivatives to the entire nation without charge for the products.

"The Program has been approved in principle by officials of the American Medical Association, American Hospital Association, Veterans Administration, Army, Navy, United States Public Health Service, the American Health Association, and others in medical and scientific fields."

The American National Red Cross is also prepared to offer to members of the College represented by the ANNALS OF ALLERGY, the services of special writers in the preparation of articles or editorial material. The organization will be glad to provide information and background material for the use of the ANNALS' staff writers who may be interested in preparing articles on the National Blood Program. The National Headquarters will also be glad to arrange to take special pictures in addition to making available glossy prints from their files. They will gladly furnish anyone interested with a "Fact Sheet" outlining the Program, setting forth the reasons for their decision for a National Blood Program, what the National Blood Program will be and what it will provide.

*(Continued on Page 98)*

**BRONCHIAL ASTHMA . .**
**HAY FEVER - URTICARIA**

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## NEWS ITEMS

*(Continued from Page 96)*

The Program includes the providing of blood and blood derivatives, without charge, to patients, physicians, and hospitals. The only charge ever made to the patient is for professional services in administering the material. In addition to whole blood plasma, the National Blood Program will provide other blood derivatives of proved value, such as: Serum Albumin, Immune Serum Globulin, Antihemophilic Globulin, Blood Grouping Serum, Fibrin Films and Thrombin, Red Cell Suspensions, and Red Cell Paste and Powder. Any blood derivatives that continued research may find useful in medicine will be made available through the Program.

* * *

The U. S. Army Medical Corps now has a number of excellent positions which can be filled by physicians who have completed their formal board requirements (residence phase) but who need one or two years of practice limited to their specialty.

There are 24 openings for Internal Medicine; 15 for Neuropsychiatry; 14 for Obstetrics and Gynecology; 11 for Radiology; 10 for Pediatrics; 7 in Anesthesia; 5 in Orthopedic Surgery, et cetera. Positions will be offered in eleven station hospitals in Germany and two in Austria.

These requirements provide excellent facilities and equipment, and a wealth of clinical material. The applicant may avail himself of this training for periods of one, two or three years. Selected applicants who hold reserve commissions in the Medical Corps, will usually be recalled to active duty in the highest grade attained prior to release from previous active service.

Eligible physicians are invited to communicate with The Surgeon General, U. S. Army, Washington 25, D. C., for further information.

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Announcement that Dr. J. P. Gray has joined the staff of Parke, Davis & Company in the capacity of Medical Consultant to the Sales and Promotion Division has been made by Harry J. Loynd, vice president of the Company.

Dr. Gray comes to Parke, Davis with an exceptional medical background. A graduate of Johns Hopkins University with an M.D. degree, and of the Harvard School of Public Health with an M.P.H., he served in public health work for many years, including posts with the United States Marine Hospital in New Orleans, the state of California and the city of San Francisco, and the Michigan Community Health Project of the W. K. Kellogg Foundation. He also is an educator, having lectured in public health at the University of California, served as dean of the School of Medicine of the Medical College of Virginia in Richmond, and also as dean of the School of Medicine, University of Oklahoma, and superintendent of the University hospitals.

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Amino acids in tablet form have been introduced by the Maltine Company, of New York City, a member firm of the American Pharmaceutical Manufacturers' Association. The new product, known as Nitramac Tablets, has overcome the taste problem by approaching it from a new direction, according to the Company. The tablet is not a disc or wafer to be chewed but is a true tablet which is swallowed whole. In this form the amino acids are carried past the taste buds by a swallow of water before they can excite a taste response.

Each Nitramac Tablet contains amino acids equivalent to 0.4 gram protein. As a dietary supplement, five tablets four times daily is a frequently prescribed dosage. Nitramac Tablets contain 19 amino acids and include all of the essential amino acids.